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Miscellaneous Agents

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HYDRAZINES AND RELATED COMPOUNDS

1. MECHANISM OF FIBRE PROPHYLAXIS OF CHEMICALLY INDUCED COLONIC CARCINOMA IN THE RAT (MEETING ABSTRACT).

Harvey JS
Department of Surgery, University Hospital of Wales, Heath Park, Cardiff CF4 4XN, England
Eur Surg Res; 13(1):96 1981

The prophylactic effect of fiber on colonic carcinogenesis may be due to a reduction in energy intake rather than an effect on stool bulk and transit time. To test this hypothesis

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colon cancer was induced in rats whose diet was varied for energy intake as well as fiber intake. 62 weanling rats were divided into four groups, matched for wt and rate of growth. All animals were given sc injections of dimethylhydrazine dihydrochloride (20 mg/kg at 10-day intervals for 150 days). The animals were housed and fed as follows until sacrificed at 170 days: group 1: normal diet ad lib, caged in fours; group 2: high fiber diet ad lib, caged in fours; group 3: high fiber diet ad lib, caged singly: group 4: normal diet restricted to the same energy, intake as group 3, caged singly. Adult mean wt with cancer incidences (in parentheses) were: group 1: 421 g (14/16); group 2: 391 g (14/16); group 3: 369 g(8/15); group 4: 358 g (10/15). There were no significant differences in cancer incidences between any of the groups taken individually and simply feeding fiber was not seen to offer any protection. Groups 1 and 2 combined had a significantly higher incidence of cancer than the smaller animals in groups 3 and 4 combined, which favors the hypothesis that any effect that fiber may have is related to cal restriction rather than to its mechanical effects in the bowel. (no Refs)

2. COLOSTOMY CLOSURE PROMOTES CELL PROLIFERATION AND DIMETHYLHYDRAZINE-INDUCED CARCINOGENESIS IN RAT DISTAL COLON.

Terpstra OT, Dahl EP, Williamson RC, Ross JS, Malt RA
(c/o Malt), Massachusetts General Hosp., Boston, MA, 02114
Gastroenterology; 81(3):475-480 1981

The influence of adaptive cell proliferation on colonic carcinogenesis was studied in male Fischer rats with a defunctioning transverse colostomy that was closed 4 wk later. Control observations were made in other rats after colonic transection, repeated at 4 wk, after laparotomy alone, or after permanent colostomy. Tumors were induced by 1,2-dimethylhydrazine (total dose, 300 mg/kg) over 11 wk, starting 2 days after the second operation. After creation of the colostomy, amounts of protein, RNA, and DNA in the distal colon halved in 4 wk (p less than 0.001), but returned to normal 7 days after restoration of colonic continuity. This reactive hyperplasia promoted the development of distal colonic carcinomas, as compared with rats having repeated transection of the bowel (incidence 32% vs 6%, p less than 0.03). Although the amounts of protein and nucleic acid in the proximal colon were unchanged by transverse colostomy, values increased by 18%-59% 4 wk after colostomy closure (p = 0.05-0.002); nonetheless, the yield of tumors in this segment was unaltered. Suture-line cancers were more common after repeat transection than after colostomy closure (76% vs 39%; p less than 0.01). These data confirm the promotional effect of increased cell proliferation on intestinal carcinogenesis. (Author abstract) (40 Refs)

3. KINETICS OF THE NON-NEOPLASTIC MUCOSA OF THE LARGE BOWEL OF DIMETHYLHYDRAZINE-TREATED RATS.

Sunter JP, Watson AJ, Appleton DR
Dept. Pathology, Queen Elizabeth Hosp., Gateshead, Tyne and Wear, NE9 6SX, England
Br J Cancer; 44(1):35-44 1981

Administration of 1,2 dimethylhydrazine (DMH) to rats by weekly sc injections causes the development of multiple epithelial tumors of the large bowel. These appear to arise as localized dysplastic abnormalities in hitherto apparently morphologically normal crypts. This study was undertaken in order to examine cell proliferation in such apparently normal crypts of DMH-treated animals. A number of proliferative abnormalities are evident, including changes in the size of the crypts, changes in the disposition of proliferating cells within them and reduced cell-cycle times. The nature and the extent of the abnormalities vary from site to site along the length of the bowel, and reflect the vulnerability of the different segments of the bowel, not only to the carcinogenic effects of DMH, but also to short-term toxicity. (Author abstract) (23 Refs)

4. THE EFFECTS OF THE CARCINOGEN, 1,2-DIMETHYLHYDRAZINE, ON TURNOVER OF 3H-THYMIDINE LABELED CELLS FROM MUCOSAL GLANDS OF MOUSE COLON.

Richards TC
Dept. Anatomy, Sch. Medicine, Univ. Oregon, Health Sciences Center, Portland, OR, 97201
Anat Rec; 200(3):299-308 1981

The compound 1,2-dimethylhydrazine (DMH), administered weekly to mice for 20 wk induces tumors in the distal segment of colon. Tumors are preceded by enlargement of the mucosal glands resulting from increases in the number of total cells and 3H-thymidine labeled cells/crypt. Cells located in the crypt base normally undergo two-three divisions as they migrate toward the lumen, and they become post-mitotic in the upper crypt. It is not known if cells in these enlarged crypts have rates of turnover similar to cells in normal crypts. Groups of w/s female mice were treated with DMH (20 mg/kg body wt) for 3, 8, or 16 wk; controls were given 0.001 M EDTA. After treatment, the animals were injected with 3H-thymidine and killed 1 hr or 1, 2, 4, 7 or 17 days later. Autoradiographs were prepared from sections of distal colon. The total cells/crypt column in 30 crypts/animals were counted. Crypts were divided into 10 equal segments based on the crypt length and the labeled cells/segment were counted. The relative number of labeled cells and the distribution of these cells within crypts were similar in DMH-treated and control animals after 1 hr. However, as the cells migrated toward the lumen, the number of labeled cells doubled after 2 days and tripled after 4 days in DMH-treated animals but only doubled during the 4 days in controls. This difference was caused by retention of an increased number of dividing cells in the lower four segments of the crypts and suggests an increase in those cells that divide twice. In addition, increased numbers of labeled cells were retained in the upper three segments of DMH-treated animals after 4 days. These findings indicate that the c rypt cells of DMH-treated animals are generally more immature than those of controls and this immaturity contributes to the enlargement of mucosal glands during carcinogenesis. (Author abstract) (22 Refs)

5. INDIRECT ALKYLATION OF CBA MOUSE LIVER DNA AND RNA BY HYDRAZINE IN VIVO. A POSSIBLE MECHANISM OF ACTION AS A CARCINOGEN.

Quintero-Ruiz A, Paz-Neri LL, Villa-Trevino S
(c/o Villa-Trevino) Departamento Investigacion, Division de Estudios, Superiores de la Facultad Medicina Universidad Autonoma de Chihuahua, Apart Postal 1506 Sucursal 'C' Chihuahua, Chihuahua, Mexico
JNCI; 67(3):613-618 1981

Treatment of inbred CBA mice with hydrazine sulfate, a liver carcinogen, plus [14C]formate or L-[methyl-14C]-methionine as a source of 'C1' units, produced [14C]7-methyl-guanine (7-MG) in liver DNA and RNA. This methylated guanine was identified by its chromatographic characteristics in three different systems: on Sephadex G10, on Dowex 50, and by paper co-chromatography with authentic 7-MG. Mice that received [14C]formate alone showed no 7-MG in their DNA or

RNA. In addition, mice treated with L-[methyl-14C]methionine alone showed no 7-MG in their DNA. These results suggest that 'indirect' alkylation of nucleic acids is a mechanism of cancer initiation by hydrazine. (Author abstract) (20 Refs)

6. FURTHER STUDIES ON THE CARCINOGENESIS OF THE COLON OF THE RAT WITH SPECIAL REFERENCE TO THE ABSENCE OF INTESTINAL CONTENTS.

Rubio CA, Nylander G

Dept. Pathology, Karolinska sjukhuset, S-104 01 Stockholm, Sweden

Cancer; 48(4):951-953 1981

The proximal and distal ends of the ascending, transverse and descending colon of 67 Sprague-Dawley rats were severed and stitched to the abdominal wall. The remaining colon was anastomosed end to end. The disarticulated colon loop was rinsed 30x over 15 days to remove all traces of intestinal contents. The animals were then given sc injections of 1,2-dimethylhydrazine (21 mg/kg body wt) for 27 wk. During that period, the isolated loops were rinsed with saline once a wk. The rats were killed after 7 mo of treatment. Eighty-five tumors developed in the 67 animals: 20 in the isolated loops and 65 in the end-to-end anastomosed colon. The carcinogen employed reached the colonic loop through the circulation and induced (independently of bile acids) mucosal changes that led to the development of colonic tumors. (Author abstract) (15 Refs)

7. COMPARATIVE MUTAGENICITY OF HYDRAZINE AND 3 METHYLATED DERIVATIVES IN L5178Y MOUSE LYMPHOMA CELLS.

Rogers AM, Back KC

Air Force Aerospace Medical Res. Lab., Wright-Patterson Air Force Base, OH, 45433

Mutat Res; 89(4):321-328 1981

The toxic and mutagenic effects of hydrazine (H), monomethylhydrazine (MMH), 1,1-dimethylhydrazine (UDMH) and 1,2-dimethylhydrazine (SDMH) were studied in cultured L5178Y mouse lymphoma cells. For range-finding toxicity experiments cells were treated for 24 hr with doses of test compound ranging from 0.1 to 15 milliM (mM) for H, MMH and UDMH and 0.1 to 25 mM for SDMH. In mutation experiments doses examined for each test compound were 0.1, 1.0, 2.5 and 5.0 mM. The toxicity studies showed that MMH was the most toxic compound, followed by H, UDMH and SDMH. Mutations were induced in L5178Y cells by H, UDMH and SDMH; treatment with MMH resulted in no significant mutation induction. All four compounds were negative in the ouabain, thioguanine and cytosine arabinoside selective systems. Results from experiments to determine the ratio of large to small clones in control and treated cultures showed that UDMH and SDMH induce proportionately more small clones. H appeared to induce equal numbers of large and small clones. The doubling times of induced and spontaneous large and small clones, isolated and maintained in nonselective medium for 10 wk, were 10-12 hr and 20-32 hr respectively. The results imply that these compounds may have different modes of action in the cell. (17 Refs)

HETEROCYCLIC COMPOUNDS

8. MASS SPECTROMETRY OF 2-SUBSTITUTED 5-NITRO-2-FURYL THIAZOLES. IDENTIFICATION OF MICROSOMAL NITROREDUCTION PRODUCTS BY ELECTRON IMPACT MASS SPECTROMETRY.

Mattammal MB, Zenser TV, Davis BB
St. Louis Veterans Admin. Medical Center, Geratric Res., Education and Clinical Center, St. Louis, MO, 63125
Biomed Mass Spectrom; 8(7):305-311 1981

The electron impact mass spectral fragmentation of nitro heterocyclic carcinogens N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide, 2-amino-4-(5-nitro-2-furyl)thiazole, 2-methyl-4-(5-nitro-2-furyl)thiazole and 2-methylamino-4-(5-nitro-2-furyl)thiazole were studied. The molecular ions undergo two modes of cleavage: one giving [M-84]+ ions which include the 2-substituted thiazole ring, while the other gives rise to the fragment [M-74]+ ions. The products of anaerobic microsomal nitroreduction of 2-methyl-4-(5-nitro-2-furyl)thiazole were isolated and purified by high-pressure liquid chromatography. The metabolites undergo different fragmentation patterns compared to the parent nitro analogs. Metabolites from anaerobic enzymatic reduction showed identical gas chromatographic, high-pressure liquid chromatographic and thin-layer chromatographic properties to the chemically synthesized material. The metabolites were identified as 1-(2-methyl-4-thiazolyl)-3-cyano-1-propenone and 1-(2-methyl-4-thiazolyl)-3-cyano-1-propanone by mass spectral fragmentation pattern. (Author abstract) (22 Refs)

9. THE MUTAGENIC ACTION OF ALIPHATIC EPOXIDES.

Voogd CE, Van der Stel JJ, Jacobs JJ
Natl. Inst. Public Health, P. O. Box 1, 3720 BA Bilthoven, The Netherlands
Mutat Res; 89(4):269-282 1981

The mutagenicity of 45 epoxides was tested on Klebsiella pneumoniae employing the fluctuation test of Luria and Delbruck. A total of 36/45 epoxides were shown to be mutagenic. In general, mutagenicity decreased with the increasing length of the carbon chain. For example, 1,2-epoxypropane was 20x more mutagenic than 1,2-epoxyhexane. Of the carcinogenic epoxides, 1,2,3,4-diepoxybutane was shown to be highly mutagenic; it increased the mutation rate of the tested strain 27x at a concentration of 1 mmole/liter. At the same concentration the carcinogen 1,2-epoxybutane increased the mutation rate 2x. Glycidaldehyde which is also a carcinogen resulted in an 69-fold increase of the mutation rate at a concentration of 1 mmole/liter. Since the mutagenic as well as carcinogenic potential of aliphatic and cyclic epoxides varies greatly, the possible dangers both to the users and to the environment of an expoxide should be assessed for each compound. (36 Refs)

10. MUTAGENICITIES OF 61 FLAVONOIDS AND 11 RELATED COMPOUNDS.

Nagao M, Morita N, Yahagi T, Shimizu M, Kuroyanagi M, Fukuoka M, Yoshihira K, Natori S, Fujino T, Sugimura T
Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan
Environ Mutagen; 3(4):401-419 1981

The mutagenicities of more than 60 flavonoids from various kinds of plants were investigated. The relationship of structure to mutagenicity is discussed on the basis of all available data on flavonoids. Among the 22 flavone derivatives tested, only wogonin was strongly mutagenic with S9 mix. This compound specifically induced mutation of TA100 with only weak activity for induction of mutation in TA98. Its action contrasted with those of most common flavonoids, quercetin and kaempferol, which preferentially induced mutations in TA98. Of the 5 flavanones, 4 flavanonols, 6 isoflavones, 4 compounds were very weakly mutagenic, inducing less than 1 revertant/nanomole with or without S9 mix to TA100, while the other 11 compounds were not mutagenic. Of the 11 miscellaneous compounds tested because of their structural relation to flavonoids, only 1 was weakly mutagenic to TA100, while the other 10 were not mutagenic. Among 55 naturally occurring flavonoid aglycones tested, wogonin, galangin, kaempferol, quercetin, rhamnetin, and isorhamnetin were strongly mutagenic to TA100 and TA98. (72 Refs)

11. NATURALLY OCCURRING MAMMALIAN LIGNANS (MEETING ABSTRACT).

Setchell KD
Division of Clinical Chemistry, Clinical Research Centre, Harrow, Middlesex, England
First International Symposium on the Podophyllotoxins in Cancer Therapy, July 8-9, 1981, South Hampton, England. Mead Johnson 51 pp., 1981.

Lignans are uncommon plant constituents but have received attention because many plant lignans and synthetic analogs have been shown to exhibit antimitotic activity and have therefore been investigated as potential anticancer agents. Recently a number of naturally occurring mammalian lignans were identified for the first time in the urine, bile and feces of humans, monkeys, and rats. Two of the prinicipal compounds, identified by gas chromatography-mass spectrometry and nuclear magnetic resonance spectrometry as trans-2,3-bis(3-hydroxybenzyl) butyrolactone and 2,3-bis(3-hydroxybenzyl)butane-1,4-diol were of novel structure. Their racemic nature excluded a direct dietary origin since all known plant lignans exist in optically pure forms. Studies of the physiological characteristics of these new compounds showed that they were present in human urine in relatively high levels almost exclusively as the glucuronide conjugate and that they exhibited a cyclic pattern in excretion in women. Studies in rats established that they undergo an enterohepatic circulation and are produced by intestinal microflora. Selective antibiotic administration to humans has shown that anaerobic bacteria, possibly clostridia, are responsible for the production of these lignans although the biosynthetic pathway is presently unknown. Preliminary studies have indicated that the lactone has a cytotoxic effect upon human lymphoid cells. These observations raise the question of whether lignans play a role as anticancer agents or whether by the nature of their chemical structure they may be carcinogenic. (no Refs)

12. EVIDENCE THAT BENZO(A)PYRENE-RESISTANT, ARYL HYDROCARBON HYDROXYLASE-DEFICIENT VARIANTS OF MOUSE HEPATOMA LINE, HEPA-1, ARE MUTATIONAL IN ORIGIN.

Hankinson O
Lab. Biomedical and Environmental Sciences, Univ. California, Los Angeles, CA, 90024
Somatic Cell Genet; 7(4):373-388 1981

The ability of treatment with known mutagens to increase the frequency of benzo(a)pyrene resistant (BPr) variants was examined. The phenotypic stability of the variants was studied as a function of time in culture and with respect to the degree of heterogeneity among subclones. The in vitro heat lability of the aryl hydrocarbon hydroxylase (AHH) was examined. All strains used were derivatives of the subclone Hepa-1c1c7 of the mouse hepatoma line Hepa-1. Four agents with three distinctly different modes of mutagenic action were used: N-methyl-N'-nitro-N-nitrosoguanidine and ethyl methanesulfonate (alkylating agents), ICR-191G (frame-shift mutagen), and UV light were used. Except for one experiment in which ethyl methanesulfonate only gave a marginal response, the mutagens consistently increased the frequency of BPr clones in a dose-dependent manner. A positive correlation was observed between the frequencies of thioguanine-resistant and BPr clones produced. Many BPr clones possessed considerably reduced, or undetectable AHH activities. Even in those variants that retained considerable AHH activity, heterogeneity in AHH activity among cells of the variants was relatively slight. The sensitivity of BPr variants to the mutagen used for their isolation is described. The in vitro temperature lability of AHH activity in certain BPr variants is discussed. (8 Refs)

INORGANIC AGENTS AND PARTICULATES INCLUDING FIBERS

13. EPIDEMIOLOGY OF ASBESTOS-RELATED TUMORS.

Newhouse M
London Sch. Tropical Medicine and Hygiene, Keppel St. (Gower St.), London WC1 E7HT, England
Semin Oncol; 8(3):250-257 1981

Tumors shown to be related to the exposure of various asbestos dusts include mesothelioma of the pleura and peritoneum, a rare tumor in the general population but an important cause of death in particular asbestos workers; bronchogenic carcinoma; and possibly gastrointestinal tumors and cancer of the larynx. A case control study of patients dying of mesothelioma at The London Hospital since 1916 revealed that in addition to occupational exposure, domestic contact with dust was also important in the pathogenesis of mesothelioma. It was shown that increasing severity of exposure and increasing length of exposure were associated with an increased death rate from mesothelioma. Factors influencing the incidence of mesothelioma are the concentration of dust to which the workers were exposed, the length of time exposed, and the predominant type of asbestos fibers used. A synergistic effect of cigarette smoking and asbestos exposure on lung cancer has particularly important implications for asbestos workers. A strong anticancer antismoking campaign and careful screening of asbestos workers for lung cancer and mesothelioma are advocated. Other asbestos-related tumors, gastrointestinal cancers and cancer of the larynx warrant further investigation to define the relative risk and to determine what, if any, other cocarcinogenic factors may be involved. (37 Refs)

14. FIBROUS ZEOLITES AND ENDEMIC MESOTHELIOMA IN CAPPADOCIA, TURKEY.

Lilis R
Environmental Sciences Lab., Mount Sinai Sch. Medicine, One Gustave L. Levy Pl., New York, NY, 10029
JOM; 23(8):548-550 1981

The carcinogenic effects of asbestos fibers is well documented. In a small, restricted area of Cappodocia, Turkey a very high rate of mesotheliomas, occurring under conditions that suggest asbestos as the cause, has been studied. Asbestos has not been found as the cause. Investigation has suggested that a variety of zeolites with fiber sizes and shapes similar to asbestos may also be carcinogenic. (6 Refs)

15. MINERALOGY OF ASBESTOS: THE PHYSICAL AND CHEMICAL PROPERTIES OF THE DUSTS THEY FORM.

Pooley FD
Dept. Mineral Exploitation, Univ. Coll., Newport Road, Cardiff CF2 1TA, Wales
Semin Oncol; 8(3):243-249 1981

The term asbestos refers to only six fibrous silicates, the fibrous amphibole minerals crocidolite, amosite, anthophyllite, tremolite, and actinolite, and the fibrous serpentine mineral, chrysotile. Each of these substances is discussed with respect to structure, production, and chemical properties. Amphibole and serpentine asbestos minerals differ markedly in physical and chemical properties. Animal experimentation has shown that only their size and shape are implicated in the ability of these particles to induce mesothelioma. While the most reactive mineral is crocidolite, all asbestos minerals produce mesothelioma in rats after ip inoculation. In inhalation studies, chrysotile produces more mesothelioma than crocidolite. The crystal structure and chemical composition of the various fibrous materials were not involved in the carcinogenic process, or were not as important as the physical shape and configuration. An increasing incidence of lung cancer has been demonstrated from exposure to all types of asbestos, and the incidence is increased by cigarette smoking. Problems in interpreting epidemiologic studies are discussed. (41 Refs)

16. CHEMICAL CHARACTERIZATION OF DIRECT-ACTING AIRBORNE MUTAGENS: THE FUNCTIONAL GROUP.

Talcott RE, Harger W
Div. Toxicology and Physiology, Dept. Entomology, Univ. California, Riverside, CA
Mutat Res; 91(6):433-436 1981

The chemical nature of the functional group involved in mutagenesis caused by airborne substances was investigated. Air particulates from Durham, North Carolina was sampled, extracted with acetone, and analyzed by a) chromatography for primary aromatic amines and b) bioassay with Salmonella typhimurium TA98 as the target organism. Following reduction with sodium borohydride-copper(II) acetylacetonate, the air extracts were again tested for amines and bioassayed. Chemical reduction of five extracts eliminated liver-independent (directly acting) mutagenic activity, and clearly produced amines in the two samples taken during cold weather. The loss of mutagenesis after reduction, and its retrieval in amine-rich extracts upon oxidation, suggest that a major portion of the total mutagenic activity in air pollution particles is contributed by nitro-substituted compounds detectable as their corresponding amines. The mutagenic burden may increase in the winter mo as the air becomes enriched with nitroaromatic substances. (11 Refs)

17. RELATIONSHIP OF THE RAW WATER QUALITY TO MUTAGENS DETECTABLE BY THE AMES SALMONELLA/MICROSOME ASSAY IN A DRINKING-WATER SUPPLY.

Grabow WO, Van Rossum PG, Grabow NA, Denkhaus R
Natl. Inst. Water Res., Council for Scientific and Industrial Res., P. O. Box 395, Pretoria 0001, South Africa
Water Res; 15(9):1037-1043 1981

The relationship of mutagens detectable by the Ames test to other properties of the Parys, South Africa drinking water supply before and after conventional treatment was studied. The raw water intake was from the Vaal River, subject to pollution with partially purified waste water (nonchlorin ated) containing high concentrations of mutagens. Information was obtained on mutagen activity, mutagen formation during conventional water treatment, properties of raw water affecting mutagen concentration in the treated water, and the relation of Ames test results to chemical quality parameters. Mutagens formed during treatment consisted mainly of neutral organic compounds inducing frameshift mutations without liver activation. Although no health hazard was inferred, the results make evident the need for surveillance of potential carcinogens in conventionally treated water taken from a polluted source. (33 Refs)

18. ELECTRON-TRANSPORT CYTOCHROME P-450 SYSTEM IS INVOLVED IN THE MICROSOMAL METABOLISM OF THE CARCINOGEN CHROMATE.

Garcia JD, Jennette KW
(c/o Jennette) Dept. Chemistry, Dartmouth Coll., Hanover, NH, 03755
J Inorg Biochem; 14(4):281-295 1981

Metabolism of the carcinogen chromate by microsomes from rats pretreated with phenobarbital (PB) or 3-methylcholanthrene (MC) with NADPH or NADH cofactor was studied. PB or MC microsomes showed similar turnover numbers, kcat, to that for controls, when NADPH was a cofactor. The value for the dissociation constant km for PB microsomes with NADPH was significantly less then that for MC and controls. Thus the second-order rate constant, kcat/km for PB was 25% greater than for MC and controls. Increased levels of P-448 had no effect on chromate reduction. With NADH as cofactor, PB and MC treatment had no effect. The rate of chromate reduction by PB microsomes with NADPH was decreased in the presence of 2'-AMP, an inhibitor of NADPH-cytochrome P-450 reductase. High concentrations of 2'-AMP also inhibited NADH-cytochrome b5 reductase activity. These reductases were also inhibited by 3-pyridinealdehyde-NAD. Metyrapone, which binds to both oxidized and reduced forms of some P-450 species, and carbon monoxide, which bonds to the ferroheme of all forms of reduced cytochrome P-450, both inhibited chromate reduction by PB microsomes with NADPH. The results indicate that the cytochrome P-450 system is involved in the reduction of chromate in microsomal systems, and thus in the activation of inorganic carcinogens. (70 Refs)

AMIDES, CARBAMATES AND UREAS

19. RAPID DEVELOPMENT OF LARGE NUMBERS OF ALPHA-FETOPROTEIN-CONTAINING 'OVAL' CELLS IN THE LIVER OF RATS FED N-2-FLUORENYLACETAMIDE IN A CHOLINE-DEVOID DIET.

Sell S, Leffert HL, Shinozuka H, Lombardi B, Gochman N
Dept. Pathology, Univ. California San Diego Medical Sch., La Jolla, CA, 92093
Gan; 72(4):479-487 1981

Fischer rats, fed 0.05% w/w N-2-fluorenylacetamide in a choline-devoid diet for 2 wk, developed a massive infiltration of the liver by small 'oval' cells. This occured rapidly 1 wk after feeding the diet for 2 wk. All of the rats fed the choline-devoid diet died within 5 wk, with massive oval cell infiltration of the liver. Although similar changes occurred in rats fed N-2-fluorenylacetamide in a choline-supplemented diet, the degree was much less. In rats fed a choline-devoid diet without N-2-fluorenylacetamide, proliferation of hepatocytes, but not of oval cells, was observed. Because the carcinogen-enhancing effects of choline-devoid diets seem to exceed those of partial hepatectomy, such diets may work by causing changes distinct from those induced by partial hepatectomy. Many oval cells contain alpha-fetoprotein, and the rapid oval cell increase is associated with an exponential increase in serum alpha-fetoprotein concentration. These observations suggest that a cellular change, not an alteration of gene expression in parenchymal cells, is the primary cause of hyper-alphafetoproteinemia during the course of chemical carcinogenesis in rats. (Author abstract) (40 Refs)

20. INCREASE OF T CELLS IN THE LIVER DURING HEPATOCARCINOGENESIS WITH N-2-FLUORENYLACETAMIDE IN RATS.

Okita K, Ando K, Fukumoto Y, Miyazaki M, Tsubota W, Kodama T, Takemoto T
Dept. Internal Medicine, Yamaguchi Univ. Sch. Medicine, 1144 Kogushi, Ube 755, Japan
Gan; 72(4):610-614 1981

The localization of thymus-derived lymphocytes (T cells) was investigated in rat liver by the immunofluorescence method during hepatocarcinogenesis with N-2-fluorenylacetamide. In the early stage of carcinogenesis, the number of T cells never increased significantly in livers in which hyperplastic liver nodules (population I) were seen. On the other hand, in the late stage of carcinogenesis, T cells extensively invaded hyperplastic nodules (population II) as well as hepatomas. According to the concept of cell-mediated immunity, hyperplastic nodules in the late stage might have a neoantigen(s) which evokes the response of T cells. Therefore, it may be concluded that populations I and II are biologically distinct lesions in spite of their histological identity. (Author abstract) (13 Refs)

21. SPECIES DIFFERENCE IN LIVER MICROSOMAL AND CYTOSOLIC ENZYMES INVOLVED IN MUTAGENIC ACTIVATION OF N-HYDROXY-N-2-FLUORENYLACETAMIDE.

Kaneda S, Seno T, Takeishi K
(c/o Takeishi) Dept. Immunology and Vitology, Saitama Cancer Center Res. Inst., Ina-machi, Saitama-ken 362, Japan
JNCI; 67(3):549-555 1981

The mutagenic activations of N-hydroxy-N-2-fluorenylacetamide (N-OH-2-FAA) by subcellular fractions of the livers of rat, the mouse, guinea pig, hamster and monkey were examined for sensitivity to paraoxon, which inhibits a deacetylase but not an arylhydroxamic acid acyltransferase. The mutagenic activation by liver microsomes was almost entirely mediated by a paraoxon-sensitive enzyme in all the animals tested. In contrast the mutagenic activation by liver cytosol was mediated mostly by a paraoxon-sensitive enzyme in mice and guinea pigs, mostly by a paraoxon-resistant enzyme in rats and hamsters, and by both enzyme types in the monkey. In rats and guinea pigs, attempts were made to identify the enzymes causing mutagenic activation in the liver cytosol by a comparison of the elution positions of these enzymes in gel filtration and DEAE-cellulose column chromatography with those of known enzymes. In the rat liver cytosol, the mutagenic activation was mediated not only by acyltransferase but also by an unknown enzyme, which was resistant to paraoxon and differed from acyltransferase in chromatographic behavior. In the guinea pig liver cytosol, the activation was due to deacetylase activities, which could be separated into four fractions by gel filtration. These data indicate that species differ in the kinds of liver cytosolic enzymes involved in mutagenic activation of N-OH-2-FAA but not in the kind of liver microsomal enzyme involved. (Author abstract) (31 Refs)

22. DIFFERENCES IN SUSCEPTIBILITY TO THE CARCINOGENIC ACTION OF URETHANE IN HYBRID MICE (C57BL/6J X C3HF) F1 (B6C3) AND (C57BL/6J X BALB/C) F1 (B6C) (MEETING ABSTRACT).

Dragani TA, Sozzi G, Della Porta G
Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy
Tumori; 67(2,SupplA):59 1981

Beginning of the 10th day of life hybrid B6C3 and B6C mice were treated qod x 5 with ip urethane in dose of 1 mg/kg. The animals were kept under observation until they reached 8 wk of age. On macroscopic examination tumors were observed in more than 90 per cent of the animals treated. Thymic lymphomas appeared with greater frequency in the B6C3 hybrid with no difference between the sexes (54 per cent in the males, 62 per cent in the females). In the B6C hybrid this type of tumor developed more often in the females (17 per cent in the males, 28 per cent among females). Liver tumors were observed in both hybrids. They appeared sooner in the B6C3 than the B6C hybrid and no noteworthy differences between the sexes were observed whereas in the B6C hybrid females proved less susceptible. Macroscopic examination revealed lung tumors in just the B6C hybrid mice which were not especially susceptible to induction of this type of tumor (78 per cent in males, 68 per cent in females). Lung tumors were seen after the first yr of age when a considerable proportion of the B6C3 animals had already died as a result of thymic lymphomas or liver tumors. The preliminary data collected support the conclusion that both hybrids are especially suited to chemical carcinogeneis studies since they are susceptible to the induction of different types of tumors. The B6C3 hybrid inherits high susceptibility to liver carcinogenesis from its C3Hf father, while the B6C hybrid inherits its high susceptibility to pulmonary carcinogenesis from its BALB/c father. (no Refs) (In ITA)

23. NATURAL KILLING AND CYTOSTASIS IN CARCINOGEN TREATED MICE AND IN MICE BEARING PRIMARY TUMORS (MEETING ABSTRACT).

Ehrlich R, Efrati M, Witz IP
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Immunobiol; 159(1/2):135 1981

In the present study we measured cytostasis and natural killer (NK) activities mediated by splenocytes from the following groups of female mice; 1) Untreated mice from several inbred strains; 2) C3HeB mice after forced breeding, a procedure inducing the formation of mammary tumors in about 70 percent of the mice; 3) BALB/c mice recipient of a pituitary isograft; 4) BALB/c mice after treatment with urethane or with dimethylbenzanthracene (DMBA); and 5) C3HeB and BALB/c mice bearing primary tumors. The results indicated that NK activity and cytostasis are found in normal mice from almost all mouse strains tested. These activites are apparently mediated by different cell populations. The cytostasis-mediating cells are non-phagocytic; express Fc gamma receptors; lack Thy-1; partially adhere to sephadex G-10 columns; do not lose activity after incubation at 37C; are present in old mouse populations and are resistant to carrageenan and hydrocortisone application in-vivo. The NK activity in group 2 and in group 3 is elevated compared to virgin mice. NK activity of BALB/c mice decreases shortly after DMBA but not after urethane treatment. DMBA-mediated suppression in NK activity can be restored by in-vivo treatment of the mice with interferon. There is a spontaneous restoration of this activity before the appearance of tumors. A decreased NK activity is found also in group 5, but not in those with lung adenomas. The cytostatic activity is not changed in tumor bearing CeHeB mice but is significantly elevated in BALB/c mice bearing primary DMBA induced tumors. Other results indicated the possibility that NK activity in group 5, but not in group 2, are regulated by non-phagocytic suppressor cells which express no Thy-1 antigen, but adhere to sephadex G-10 columns. Mixing experiments indicated that such suppressor cells have the ability to inhibit NK activity of normal splenocytes from syngeneic or allogeneic mice. (no Refs)

ALIPHATIC HALOGEN COMPOUNDS

24. DNA DAMAGE BY HALOALKANES IN HUMAN LYMPHOCYTES CULTURED IN VITRO.

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Cancer Lett; 13(3):213-218 1981

A study is presented of the action of seven haloalkanes as toxic or DNA damaging agents on human lymphocytes. The parameters studied were the scheduled (replicative) and unscheduled (reparative) DNA syntheses seen as tritiated thymidine [(3h)TdR] uptake in a well-known short-term (4 hr) culture system with or without metabolic activation (use of S-9 mix). The toxic effects of the substances were measured by (3H)TdR uptake for the scheduled DNA synthesis (SDS). The effect of the haloalkanes as DNA damaging agents was studied with the use of (3H)TdR for uptake of unscheduled DNA synthesis (UDS) and was determined by adding 10 mM hydroxyurea to the culture to block (3H)TdR uptake due to SDS. Metabolic activation was achieved by the method of Ames et al. At the end of the culture period (3H)TdR uptake by the lymphocytes for SDS or UDS was determined by a liquid scintillation spectrometer. When the haloalkanes were added to the wells in a concentration of 5 ug/ml, 1,2-dibromoethane (DBE), trichloroethylene (TCE), carbon tetrachloride (CTC), and chloromethyl methyl ether (CMME) exerted the greater toxic effects whereas the uptake of (3H)TdR in the presence of 1,2-dichloroethane (DCE), chloroform (TCM), and dichloromethane (DCM) was similar to that of the controls. In a second study with incubation of the agents with 10 mM hydroxyurea, addition of the activation mixture only markedly increased (3H)TdR uptake in the cases of CMME and DBE. The results indicate the CMME, DBE, TCE and DCE elicit DNA reparative synthesis in human lymphocytes, indicative of their mutagenic power. Low or negative values of UDS were observed for CTC, DCM and TCM. The values on UDS and SDS found were generally not dose-dependent. (14 Refs)

25. LACK OF MUTAGENIC EFFECTS OF HALOTHANE IN MAMMALS IN VIVO.

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Anesthesiology; 55(2):143-147 1981

Rodents were exposed in vivo to various clinical doses of halothane to observe structural chromosome aberrations, micronuclei, sister chromatid exchanges (SCEs), dominant lethal mutations, and interferences with phases of the cell cycle. The frequency of chromosome aberrations in bone marrow cells was not increased after exposing Chinese hamsters to 1% halothane once for 3 hr, twice for 3 hr (exposures 24 hr apart), or to 0.5% for 24 hr. The analysis of SCEs in bone marrow cells were also negative after exposing hamsters to 1% halothane for 3 hr, or to 0.5% for 12 hr. In halothane-exposed female mice (0.75% for 16 hr), oocyte maturation (meiotic stages) was delayed. Another group of exposed female mice (1% for 5 hr) were mated with untreated males. The number of dead implants was not increased as compared to controls. In liver cells of 16-day-old living embryos, neither monosomic nor trisomic cells were observed. Male mice were exposed to 1% halothane for 1 hr per day for 48 days. On the evening of the 48th they were mated with untreated females. Dominant lethal mutations were not increased as compared to controls. In RBC of these chronically exposed male mice, the frequency of micronuclei was not significantly enhanced. The authors conclude that halothane does not induce mutations under the in vivo conditions tested in this study. (Author abstract) (21 Refs)

POLYHALOGENATED RING COMPOUNDS INCLUDING INSECTICIDES

26. PESTICIDES: MUTAGENIC AND CARCINOGENIC POTENTIAL.

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ACS Symp Ser; 160:89-113 1981

A phased approach has been developed for evaluating the mutagenic and carcinogenic potential of chemicals. The method combines cost-effective use of limited testing facilities with protection from hazards to human health. Since no single test is capable of detecting all hazardous chemicals, proper testing requires the minimum number of tests which will effectively reveal mutagenic and carcinogenic properties. Phase I involves detection. Short-term bioassays emphasize point mutations and primary DNA damage in species and chromosomal changes in mammalian cells. Phase II tests are used to confirm the results of Phase I. More expensive tests use narrower and more definitive bioassays in cultures, plants, insects, and mammals. Chemicals are tested for both mutagenicity and carcinogenicity. Phase III assesses the risk involved with a chemical. Whole-animal bioassays are used to determine quantitative hazards. Within Phases I and II a 'core battery' of tests is used to indicate a probable negative result, thus eliminating unnecessary testing. The phased approach has been used to test 38 pesticides. The results are discussed as an illustration of how the method works. (71 Refs)

27. LIVER TUMORS INDUCED IN WISTAR RATS FOLLOWING COMBINED ADMINISTRATION OF DDT AND PHENOBARBITAL (MEETING ABSTRACT).

Barbieri O, Sanguineti M, Rossi L
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Tumori; 67(2,SupplA):60 1981

Prolonged administration of dichlorodiphenyltrichloroethane (DDT) and phenobarbital (PB) induces liver tumors (hepatomas) in rats in advanced age in terms of their life span (80 wk and beyond). In the present experiment we wished to determine whether combined long-term treatment with DDT and PB reduces latency and/or favors progression of these tumors as opposed to more malignant types. Eighty male and female Wistar rats were exposed to DDT (500 ppm in the diet) and PB (500 ppm in their drinking water) till 150 wk of age. An equal number of rats was used as a control. The most significant results of this experiment are as follows: 1) liver tumors were induced only in animals in advanced age (latency unaltered); 2) combined treatment caused induction of several hepatocarcinomas while among the hepatomas observed many contained cystic conglomerates (degenerative formations not seen during separate treatment); 3) an additive effect of the 2 compounds was observed in females (83 per cent liver tumors as opposed to 55 per cent in females exposed to DDT and 32 per cent among those exposed to PB), while the incidence of such tumors remained unaltered in the males (59 per cent compared to 59 per cent with PB and 35 per cent with DDT). The observations reported clearly indicate that DDT and PB have the effect of potentiating carcinogenesis in experimental animals when administered simultaneously. That is of great importance since in human surroundings there is a prevalence of weak chemical carcinogens. Our results suggest that interaction between these compounds and human tissues may increase the oncogenic risk in our species. (no Refs) (In ITA)

28. POLYHALOGENATED BIPHENYLS AND PHENOBARBITAL: EVALUATION AS INDUCERS OF DRUG METABOLIZING ENZYMES IN THE SHEEPSHEAD, ARCHOSARGUS PROBATOCEPHALUS.

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Chem Biol Interact; 36(2):229-248 1981

Several doses of Aroclor 1254 (polychlorinated biphenyl (PCB) mixture), Firemaster FFl (polybrominated biphenyl (PBB) mixture), 2,2',4,4',5,5'-hexabromobiphenyl (HBB), 3,3',4,4',5,5'-hexachlorobiphenyl (HCB) and phenobarbital (PB) were administered to the marine fish sheepshead (Archosargus probatocephalus). The PCB and PBB mixtures caused induction of hepatic microsomal benzo[a]pyrene hydroxylase (AHH), 7-ethoxycoumarin O-deethylase (7-EC) and 7-ethoxyresorufin O-deethylase (ERF) activities, but not benzphetamine N-demethylase (BND), epoxide hydrolase (EH) or glutathione S-transferase (GSH-T) activities. This induction pattern is typical of that caused by polycyclic aromatic hydrocarbons (PAH) in fish and mammals or by tetrachlorodibenzo-p-dioxin (TCDD) in mammals. The extent of induction of AHH-activity and cytochrome P-450 content was higher when experiments were carried out in summer (water temperature 25 +-4 C) than in winter (water temperature 11 +-3 C). Firemaster FFl (15 mg/kg) induced fish for at least 56 days in both summer and winter at which time the liver concentrations of PBB were in the ppm range. PCB concentrations in the ppm range have been found in fish from polluted lakes and seas, thus we may expect that environmental exposure to PCB is sufficient to induce hepatic mixed function oxidase (MFO) activities. The PCB isomer 3,3',4,4',5,5'-HCB, which induces the same spectrum of hepatic drug-metabolizing activities as TCDD and PAH in rats, had a broadly similar effect in the sheepshead. Another purified isomer 2,2',4,4',5,5'-HBB, which induces the same enzymes as PB in rats, had no effect on drug-metabolizing activities in sheepshead. PB was also without effect on sheepshead hepatic drug-metabolizing enzymes, although a typical narcotic effect was produced in PB-treated sheepshead. Our studies provide further evidence that drug-metabolizing activities in fish liver are readily induced by chemicals like TCDD or PAH, but we fail to demonstrate induction after treatment of sheepshead with inducers of the PB type. (Author abstract) (48 Refs)

29. INDUCTION IN RATS OF LIVER DNA SINGLE-STRAND BREAKS BY THE POLYCHLORINATED BIPHENYL AROCHLOR 1254.

Robbiano L, Pino A
Istituto di Farmacologia dell' Universita di Genova, Genoa, Italy
Boll Soc Ital Biol Sper; 57(4):407-413 1981

Arochlor 1254 (a mixture of polychlorinated biphenyls) induces benign and malignant tumor growth in mice by prolonged administration. Mutagenic and clastogenic studies done so far gave contradictory results. Single doses of Arochlor 1254 (67, 648 or 1,295 mg/kg) given to male albino rats by gastric gavage does max damage in 4-12 hr and almost complete repair is achieved after 48 hr. Daily administration might result in a cumulative effect, because DNA damage is only partially repaired after 24 hr. Arochlor 1254 is 40 times less carcinogenic than diethylnitrosamine and is 110 times less effective in causing DNA damage. (17 Refs)

30. EPIGENETIC MECHANISMS OF ACTION OF CARCINOGENIC ORGANOCHLORINE PESTICIDES.

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ACS Symp Ser; 160:45-56 1981

Carcinogens may be divided operationally into two groups: (1) Genotoxic agents cause direct genetic damage and are a qualitative hazard. (2) Epigenetic agents do not cause genetic damage. They are a quantitative hazard, causing damage when present in high doses. The organochlorine pesticides apparently are epigenetic carcinogens. In cells derived from the liver, the target organ of organochlorine pesticides, these agents have not produced genetic mutations. Pesticides may act on the cell membrane. Several studies have indicated that they interfere with intercellular communication. Cells with abnormal genotypes then proliferate beyond the normal growth requirements of the tissue in which they occur. The apparent lack of carcinogenic effects in human populations may be due to insufficient exposure, more efficient intercellular communications in humans, or a lack of the genetic alterations in the liver necessary to give rise to neoplasms in the presence of a promoting agent. (45 Refs)

BENZENE DERIVATIVES

31. EVALUATION OF DNA DAMAGE INDUCED BY NITROCHLOROBENZENES (MEETING ABSTRACT).

Cesarone CF, Bolognesi C, Santi L
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Tumori; 67(2,SupplA):55 1981

It has been shown that the wide range of toxic effects induced by nitrochlorobenzenes in different species of laboratory animals is directly related to the number of chlorine atoms and nitro group substituents and their distribution on the aromatic ring. By means of alkaline elution we have evaluate d the damage to liver, kidney, and brain DNA in male Swiss CDI mice after treatment with mono-, di-, and trinitrochlorobenzene in graded doses (1000, 180, 60, mg/kg). All of the tissues examined had significantly greater DNA elutability than the controls. These chemical compounds, however, showed a greater organ tropism for cerebral tissue. In nervous tissue it was discovered that at equally toxic doses the increase in DNA damage was directly proportional to the number of nitro groups present on the molecule. N-nitroso-N-methylurea (NMU), a familiar cerebral carcinogen, was used as a positive control. On the basis of this comparison the damage caused by doses of dinitrochlorobenzene and trinitrochlorobenzene equal to 60 mg/kg is comparable to the damage caused by doses of NMU equal to 100 and 150 mg/kg, respectively. The high specificity of nitrochlorobenzenes for nervous tissue is probably due to its high lipid content which, as in the liver and skin, represents the location of compounds insoluble in water. The concentration of active metabolites of these derivatives in these organs may reach particularly high levels and hence represent a high potential for toxicity. (no Refs) (In ITA)

DRUGS, COSMETICS, DETERGENTS AND OTHER COMMERCIAL MATERIALS

32. PHOTOLABILITY OF BLEOMYCIN AND ITS COMPLEXES.

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Cancer Lett; 13(3):265-268 1981

Photo-induced reactions of bleomycin were studied with a medium-pressure mercury lamp. The experiments were conducted at 22 C, in 0.05 M MES buffer and at pH 7.0. A relatively rapid decomposition was indicated by a decrease in absorbance at approx 290 nanometer (nm) over the first approx 8 min; an isosbestic point was found at 319 nm. The subsequent process took about an hr until a new absorption band was reached at approx 340 nm. A separate study of the faster primary process indicated a transitory isosbestic point at approx 270 nm. Employing a wavelength window of 300-350 nm Cu(II) and Fe(II) complexes of bleomycin were also found to photolyse smoothly but more slowly than bleomycin. An increase of the DNA concentration present in a soln of bleomycin photolysing under the above conditions caused an increase in the photolysing rate. This increase, however, was not directly proportional to the amount of DNA added. It was assumed that the increased rate of photolysis in the presence of DNA indicted that the DNA bleomycin complex is more photoactive than free bleomycin. (8 Refs)

33. BLEOMYCIN-INDUCED STRAND-SCISSION OF DNA. MECHANISM OF DEOXYRIBOSE CLEAVAGE.

Giloni L, Takeshita M, Johnson F, Iden C, Grollman AP
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J Biol Chem; 256(16):8608-8615 1981

The bleomycins, a family of glycopeptides with antineoplastic activity, bind to DNA and cause strand-scission in a reaction requiring Fe(II) and oxygen. Strand-scission is accompanied by the simultaneous release of free bases and four low mol wt compounds that react with 2-thiobarbituric acid to form chromophores absorbing maximally at 532 nm. The structure of these four products was elucidated as follows: formic acid hydrolysis released thymine, cytosine, adenine, and guanine, respectively; treatment of each compound with phenylhydrazine yielded 1-phenylpyrazole. The adenine-containing compound was reduced with sodium borohydride and the trimethylsilyl derivative was prepared. High resolution mass spectrometry of this derivative revealed silylated 3-(adenin-9'-yl)-2-propen-1-ol, consistent with formulation of the original compound as 3-(adenin-9'-yl)-2-propenal. The reaction product containing thymine was similarly shown to be 3-(thymin-1'-yl)-2-propenal. The 3-substituted propenal structures proposed were confirmed by chemical synthesis. Oligonucleotides, produced by bleomycin-induced strand-scission, were found to contain glycolic acid residues esterified through the hydroxyl group to the 3'-phosphate termini. We conclude that the primary reaction products resulting from bleomycin-induced strand-scission of DNA have a common structure: Base-CH=CH-CHO. These observations are consistent with a reaction mechanism initiated by free radical abstraction of the C-4' proton of deoxyribose and leading to oxidative cleavage of the (C-3')-(C-4') bond. (Author abstract) (57 Refs)

34. SCANNING ELECTRON MICROSCOPY OF CYCLOPHOSPHAMIDE-INDUCED HYPERPLASIA OF THE RAT URINARY BLADDER (MEETING ABSTRACT).

Friedell GH
Saint Vincent Hospital, Worcester, MA
Long Term Normal Tissue Effects of Cancer Treatment, April 13-15, 1981, Bethesda, Maryland Committe for Radiation Oncology Studies; 1981

Urinary bladder damage caused by interperitoneally injected cyclophosphamide in male F344 rats was studied by light microscopy, scanning electron microscopy, and autoradiography. A dose response was evident in the number and size of lesions induced and the time of regeneration and repair. Scanning electron microscopy disclosed pleomorphic microvilli on the luminal surface of cells during the early phases of hyperplasia. The greatest number of cells with pleomorphic microvilli occurred 2, 5, and 7 to 8 days following injection of 75, 100, and 200 mg per kg of cyclophosphamide, respectively. Of the few rats surviving beyond 1 yr after a single injection, none had bladder lesions at any of the dose levels. The changes in the epithelium observed by scanning electron microscopy following cyclophosphamide injection were compared to those observed during bladder carcinogenesis. (no Refs)

35. INDUCTION OF 8-AZAGUANINE RESISTANCE AND SISTER CHROMATID EXCHANGE IN HUMAN LYMP HOCYTES EXPOSED TO MITOMYCIN C AND X RAYS IN VITRO.

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Nature; 292(5824):601-605 1981

Indirect evidence implies that 8-azaguanine-resistant (AGr) lymphocytes in human peripheral blood are mutants associated with the loss of the hypoxanthine-guanine phosphoribosyltransferase (HPRT) locus on the active X chromosome, the mutation frequency increasing linearly with age. AGr variants are readily induced in lymphocytes exposed to mitomycin C in vitro, their incidence correlating with induced sister chromatid exchanges (SCEs). Although SCE events and the development of an AGr phenotype may reflect a common type of DNA damage, mitomycin C-induced AGr variants are not mutants but are suggested to be cells having a transcriptional block at the HPRT locus. AGr variants are also readily induced by x-rays in vitro, their incidence correlates closely with the incidence of aberrations induced in the X chromosome and they are considered to have a mutational origin. (Author abstract) (38 Refs)

36. EFFECTS OF ACUTE AND CHRONIC ADMINISTRATION OF MITOMYCIN C ON THE INDUCTION OF SISTER CHROMATID EXCHANGES IN VIVO.

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Environ Mutagen; 3(4):489-495 1981

The relationship between the timing of mutagen administration, sister chromatid exchange (SCE) induction, and persistence of SCE-inducing lesions was examined using bone marrow cells from male C57BL/6J mice in vivo as the cell system and mitomycin C (MMC) as the mutagenic agent. Administration of MMC (2.5 mg/kg) 1, 6.5, and 13 hr after the onset of bromodeoxyuridine (BrdU) infusion resulted in the induction of approx 45 SCE/cell at each time point. When MMC was injected 19.5 hr after the onset of BrdU infusion, SCE levels averaged approx 17 SCE/cell. When MMC was injected 26 hr prior to BrdU infusion, only baseline levels of SCE were detected. Administration of MMC 19.5 hr prior to BrdU infusion resulted in a small but significant induction of SCE. When MMC was given 6.5 hr before BrdU labeling, an av of 25 SCE/cell was seen. Following chronic weekly or bimonthly injections involving large accumulated doses (up to 15 mg/kg), SCE levels in the treated mice were not significantly different from controls, although high MMC doses did significantly impair cell replication kinetics. The results indicated that nondividing cells are capable of removing few if any MMC-induced lesions that can result in SCE formation. However, one round of DNA replication appears to be sufficient to remove most or all MMC-induced lesions that may lead to SCE formation. (19 Refs)

37. ROLE OF TESTOSTERONE ON MITOMYCIN C INDUCED CHANGES IN TESTICULAR HISTOLOGY IN RATS.

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Indian J Exp Biol; 19(4):386-387 1981

The role of testosterone in mitomycin C (MC)-induced changes in testicular histology was studied in closed colony-bred sexually immature male rats. The data clearly showed that testicular wt was greatly reduced in MC-treated rats but was near normal in those MC-treated rats who had also received testosterone proprionate. It was suggested that testicular degeneration in MC-treated rats was not only due to damage of the genetic material in the spermatogonia but also related to testosterone physiology. (12 Refs)

38. ACTION OF VARIOUS PHARMACOLOGICAL AGENTS ON THE NUCLEAR AND CHROMOSOMAL STRUCTURES OF HUMAN LYMPHOCYTES.

Bastide P, De Rocca Serra MF, Fellmann N, Jaffray JY, Geneix A, Malet P, Turchini JP

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Cytologia (Tokyo); 46(1):387-391 1981

The effects of nine antitumoral agents (alkylating agents: nitrogen mustard, chlorethazine, cyclophosphamide (CP), and ifosfamide (IF); alkylating antibiotics: mitomycin C (MC) and actinomycin D (AD); nucleic acid inhibitors: 5-bromodeoxyuridine (5-BD) and cytarabine (Ara C); alkaloids: teniposide (TP); and others: amikelline (AK)) on nuclear and chromosomal structures were studied in human lymphocytes. TP blocked entrance into prophase, caused nuclear polymorphism, and produced thickening of chromatid strands. 5-BD and Ara C, and to a less degree MC, induced secondary chromosomal stretching and constriction. AD, CP, IF, and Ara C produced chromatid unwinding. MC and AD, and to a lesser extent 5-BD and Ara C, produced chromosomal gaps and breaks. The effects of AK on the lymphocyte nucleus are described. (7 Refs) (In FRE)

39. EFFECT OF PHENOBARBITAL ON THE DEVELOPMENT OF NEOPLASTIC LESIONS IN THE LIVER OF CYCASIN-TREATED RATS.

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J Cancer Res Clin Oncol; 100(3):231-238 1981

The effect of phenobarbital (PHE) on neoplastic lesions induced in the liver and kidney of ACI rats by a single administration of cycasin (CYC) was investigated. Rats were placed into one of four groups: Group 1 received 100 mg CYC/kg by gavage and PHE at a level of 0.05% in their diet until the termination of the experiment; Group 2 received CYC alone; Group 3 received PHE alone; and Group 4 received no treatment. In Group 1, liver tumors were induced in 1/12 males and 7/12 females and one sarcoma and one interstitial tumor of the kidney were also induced. In Group 2, one liver tumor was found in a female, and two interstitial tumors of the kidney and one jejunal adenocarcinoma were induced. In Group 3, only one interstitial cell tumor in the testis was found. In Group 4, two interstitial cell tumors in the testes, one pituitary adenoma, and one adrenocortical adenoma were found in males, and one pancreatic exocrine adenoma was found in a female. Significant numbers of gamma-glutamyl-transpeptidase (GGT)-positive foci were induced in Groups 1 and 3. In Group 2, a small number of tiny foci were seen. Many GGT-positive foci were observed in Group 4, however, they were small-sized. Thus, PHE possesses a tumor-promoting effect in terms of induction of neoplastic lesions in the liver, but not the kidney. (27 Refs)

40. GLUCOSE-6-PHOSPHATE DEHYDROGENASE AND GAMMA-GLUTAMYLTRANSPEPTIDASE ACTIVITIES IN THE LIVER DURING CHEMICALLY INDUCED HEPATOCARCINOGENESIS IN RATS AND MICE.

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Toxicol Appl Pharmacol; 60(1):26-32 1981

Male Donryu rats were divided into three groups. One group was fed a diet containing 0.06% 3'methyl-4-(dimethylamino) azobenzene (3'-Me-DAB). The second group was given 60 ppm diethylnitrosamine (DEN) in drinking water. The third group was a control. Eight-wk-old random-bred ddY mice were divided into three groups. The first was fed 0.05% o-aminoazotoluene (o-AT). The second received 0.06% 3'-Me-DAB. The third was a control. Glucose-6-phosphate dehydrogenase (G-6-PDH) and gamma-glutamyltranspeptidase (g-GTP)activities were measured over a period of wk. The hepatic levels of G-6-PDH and g-GTP increased after the start of 3-Me-DAB, DEN, or g-GTP administration, decreased once, and then showed sustained increase. Sodium phenobarbital also raised the level of G-6-PDH in rat livers. The data suggest that induction of increased G-6-PDH levels may be closely related to hepatic g-GTP activity in hepatocarcinogenesis in rats and mice. (31 Refs)

41. EFFECTS OF HEXESTROL, MEDROXYPROGESTERONE ACETATE AND CHLORMADINONE ACETATE ON 7,12-DIMETHYLBENZ[A]ANTHRACENE-INDUCED RAT MAMMARY CANCER IN RELATION TO ESTROGEN RECEPTOR.

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Dept. Surgery, Tokyo Metropolitan Komagome Hosp., Honkomagome 3-18-22, Bunkyo-ku, Tokyo 113, Japan
Gan; 72(4):604-609 1981

The effects of hexestrol (HXS), medroxyprogesterone acetate (MAP) and chlormadinone acetate (CMA) on 7,12-dimethylbenz[a]anthracene-induced mammary cancer in rats were evaluated. As a result of successive im injections of HXS at dosages of 2 or 10 mg/kg or MAP at dosages of 24 or 120 mg/kg, tumors were markedly reduced in size in all groups on day 7-day 14. These effects were the same regardless of the presence or absence of cytoplasmic estrogen receptors (ER) in tumors as determined by the dextran-coated charcoal method. Although such an effect was also seen with CMA, it was much less marked than the effects seen with HXS and MAP. The body wt of HXS-administered groups decreased considerably, whereas those of MAP-administered groups increased. These results may suggest that there is another endocrinological tumor-suppressing mechanism besides the mechanism involving the estrogen-ER system in large-dose administration of HXS and MAP. (Author abstract) (13 Refs)

42. URETHANE INDUCTION OF SISTER CHROMATID EXCHANGE (SCE) IN DIFFERENT STRAINS OF MICE (MEETING ABSTRACT).

Sozzi G, Dragani TA
Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy
Tumori; 67(2,SupplA):60 1981

C57BL/6J, BALB/c, C3Hf, DBA/2 and AKR mice were treated with ip urethane in physiologic soln with single doses of 0.150 and 300 mg/kg. One hr later a compress of 50 mg of bromodeoxyuridine (BUdR) was implanted sc, 22 hr later the animals were treated with 5 mg/kg of colcemid and sacrificed 2 hr later. Marrow-cell sampling, metaphase preparation and FPG staining were all performed by means of the usual technics. A linear dose-response relationship was noted in all of the strains. The DBA/2 proved most susceptible to sister chromatid exchange (SCE) at both doses of urethane. In the higher dose DBA/2 reached a frequency of 26.2 SCE/cell whereas strains C3Hf, C57BL/6J, AKR and BALB/c showed 22.4, 19.4, 19.1, and 18.7 SCE/cell, respectively. SCE persistence during the interval of time between treatment with 300 mg/kg of urethane and sampling of AKR and C57BL/6J strain cells was also evaluated. 30 and 48 hr after urethane administration we observed fewer SCE than after 24 hr in both strains. No significant differences were found between the 2 strains with respect to SCE frequency at 24 and 48 hr while 30 hr after treatment a higher level of SCE was observed in the AKR strain (14.0 SCE/cell) than the C57BL/6J (9.7 SCE/cell). These findings confirm that the SCE 'in vivo' is adequate for cytogenetic analyses of differences in susceptibility and permanence of damage induced by carcinogen-mutagens in strains of mice. (no Refs) (In ITA)

43. MODIFICATION OF LUNG TUMOR DEVELOPMENT IN A/J MICE.

Witschi HP, Hakkinen PJ, Kehrer JP
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Toxicology; 21(1):37-45 1981

Male and female A/J mice (age 6-8 wk) were divided into five groups with controls. The first group received 500 mg/kg urethan ip. One wk later weekly injections of 300 mg/kg butylated hydroxytoluene (BHT), 500, 300, or 150 mg/kg butylated hydroxyanisole (BHA), or 1,000 mg/kg vitamin E began. The second group received either 10 mg/kg 3-methylcholanthrene (3-MC), 2 injections 1 wk apart, or 7 mg/kg dimethylnitrosamine (DMN), given once. After 1 wk 4 weekly injections of 300 mg/kg BHT were begun. The third group received 500 mg/kg urethan ip, followed after 1 wk by 80 mg/kg methylcyclopentadienyl manganese tricarbonyl (MMT). The fourth group received 400 mg/kg BHT, followed immediately by either a single injection of urethan or a continuous exposure to urethan. The last group received 400 mg/kg BHT followed after 2 wk by either 1,000 or 500 mg/kg urethan. The results show that BHT enhances the development of tumors induced by urethan, 3-MC, or DMN. BHA and vitamin E did not have this effect. MMT produced cell proliferation, but did not enhance carcinogenesis. Apparently the antioxidant property of BHT was not related to effect on tumor development. Rapidly dividing lung cells were not more susceptible to tumor development than resting lung cells. (21 Refs)

44. METABOLIC ACTIVATION AND MUTAGENICITY OF 4 VINYLIC MONOMERS (VINYL CHLORIDE, STYRENE, ACRYLONITRILE, BUTADIENE).

Duverger M, Lambotte M, Malvoisin, De Meester C, Poncelet F, Mercier M
(c/o Poncelet) Lab. Biotoxicology, Univ. Louvain Sch. Pharmacy, U.C.L.-73 69, B. 1200 Brussels, Belgium
Toxicol Eur Res; 3(3):131-140 1981

Literature data on the mutagenic activity and metabolism of monomers vinyl chloride (VCM), styrene (STY), acrylonitrile (ACN) and butadiene (BUT) are reviewed. Vinylic monomers were shown to be susceptible to metabolic conversion by the mixed function oxidase of the endoplasmic reticulum into primary reactive intermediates (oxiranes). VCM, STY, ACN, and BUT were mutagenic in Salmonella typhimurium test system. VCM was shown to induce recessive lethals in Drosophila melanogaster. Incubation of Chinese hamster cells with VCM produced a dose-dependent mutagenicity and cytotoxicity. An increased frequency of chromosome aberrations was recorded in workers who had an occupational exposure to VCM and STY. (130 Refs)

45. FOLLOW-UP STUDY ON THE CARCINOGENICITY OF VINYL CHLORIDE AND VINYLIDENE CHLORIDE IN RATS AND MICE: TUMOR INCIDENCE AND MORTALITY SUBSEQUENT TO EXPOSURE.

Hong CB, Winston JM, Thornburg LP, Lee CC, Woods JS
(c/o Woods) Battelle Seattle Res. Center, 4000 N.E. 41st St., Seattle, WA, 98105
J Toxicol Environ Health; 7(6):909-924 1981

The development and incidence of neoplastic changes and other effects during a 12-mo exposure follow-up period in male and female albino CD-1 mice and CD rats exposed to vinyl chloride (VC) or vinylidene chloride (VDC) for various lengths of time were evaluated. Eight to 28 mice of each sex and 4-16 rats of each sex were exposed to 50, 250, or 1,000 ppm VC, 55 ppm VDC, or filtered air for 6 hr/day, 5 days/wk. Exposure of mice and rats to VC for 1, 3, and 6 mo and 1, 3, 6, and 10 mo, respectively, increased the number of deaths and increased moribundity at all dose levels during the exposure and postexposure periods. The cumulative tumor incidence for essentially all organ sites in animals exposed to 50 ppm VC or 55 ppm VDC was similar to that in controls (except for mammary gland tumors in female mice). Only at higher dose levels of VC did significant increases in cumulative tumor incidence occur. Cumulative tumor incidence during the period after VC exposure increased with duration of exposure, independent of dose level. The implication of the findings with respect to the assessment of cancer risk resulting from exposure of humans to VC and perhaps other carcinogens is discussed. (23 Refs)

46. CARCINOGENIC ACTIVITY OF POLYVINYL CHLORIDE.

Costa V, Frongia N
I Cattedra di anatomia e istologia patologica, Universita di Cagliari, Cagliari, Italy
Pathologica; 73(1023):59-67 1981

Thirty rats were treated with polyvinyl chloride (PVC): 200 mg/day po for 7 mo beginning on day 30 of life), after which 1 g PVC was given. Two rats developed sc fibrosarcoma fibrosarcoma within 550 days. One of the two animals also developed a malignant lymphoreticular tumor of the lung. (17 Refs) (In ITA)

47. EVALUATION OF THE GENETIC ACTIVITY OF INDUSTRIALLY PRODUCED CARBON BLACK.

Kirwin CJ, LeBlanc JV, Thomas WC, Haworth SR, Kirby PE, Thilagar A, Bowman JT, Brusick DJ
Phillips Petroleum Co., B-57 AB, Bartlesville, OK, 74004
J Toxicol Environ Health; 7(6):973-989 1981

The mutagenic potential of a single sample of oil furnace, N-339 carbon black (NCB), was studied in five assays. In the Salmonella assay, NCB did not cause significant increase in the reversion index of any of the tester strains with or without metabolic activation by rat liver microsomes. Three of the six dose levels of NCB were associated with statistically significant increases in sister chromatid exchange frequencies, but these appeared to be due to the slightly lower than normal frequency in the solvent culture medium. Cellular toxicity was exhibited in the nonactivated system for the mouse lymphoma assay at 50,000 ug/ml NCB. The activated system exhibited cellular toxicity at 10,000 ug/ml. At 50,000 ug/ml both systems produced at least 99% cell death. Over a wide range of concentrations, NCB did not induce any significant increase in mutant frequencies in the L5178Y mouse lymphoma assay. The cell transformation assay showed the desired cellular toxicity of more than 50% reduction in relative cloning efficiency with NCB. A dose of 16,384 ug/ml NCB reduced relative cloning efficiency to 38%. In the C3H/10T1/2 cell transformation assay, NCB did not cause morphological transformation of cells, while the positive control, dimethylbenzanthracene, exhibited the expected positive results. In the Drosophila assay, designed to detect point mutation, NCB did not induce significant genetic damage under test conditions. The results indicated that NCB does not exhibit any significant genetic activity in the five short-term genetic activity assays perf ormed. (40 Refs)

48. INHALATION ANESTHETIC DRUG PRODUCTS; PROPOSED REVOCATION OF REQUIREMENTS FOR STUDIES OF CARCINOGENIC AND TERATOGENIC POTENTIAL.

Food and Drug Administration
Bureau of Drugs, (HFD-30) Food and Drug Administration, 5600 Fishers Lane, Rockville, MD, 20857
Fed Regist; 46(167):43465-43466 1981

The Food and Drug Administration's (FDA) proposal to revoke the regulation that requires manufacturers to conduct studies in animals of halogenated inhalation anesthetic drug products to determine the potential of these drug products to cause cancer and birth defects was reported. Although the FDA believes that section 310.511 is authorized, the agency is proposing to revoke the requirements on the basis that they no longer appear to be necessary. The research that was the original basis for the regulation was found to be deficient, and further studies that have been made since the regulation was announced indicate that the studies required by section 310.511 are not necessary. Revocation of the regulation was thought to have no significant effect on the human environment, therefore an environmental impact study will not be prepared. (8 Refs)

49. CO-MUTAGENIC EFFECTS OF 2-AMINOANTHRACENE AND CIGARETTE SMOKE CONDENSATE ON SMOKER'S URINE IN THE AMES SALMONELLA ASSAY SYSTEM.

Hannan MA, Recio L, Deluca PP, Enoch H
McDowell Cancer Network, Univ. Kentucky, Lexington, KY, 40536
Cancer Lett; 13(3):203-212 1981

Cigarette smoke condensate (CSC), benzo[a]pyrene, and aromatic amine 2-aminoanthracene (2-AA) were shown to be indirect mutagens in the TA98 strain of Salmonella typhimurium. The combination of CSC and 2-AA had a synergistic effect on histidine reversion. The enhancement of the mutagenic activity of 2-AA by CSC in TA98 salmonella was dose-dependent. The co-mutagenic effect of CSC was shown to be specific. No comutagenic effect was exhibited when CSC was in combination with either ethylmethane sulfonate, methylmethane sulfonate, or 9,10-dimethyl-1,2-benzanthracene. In order to investigate the factor(s) in CSC that are responsible for the co-mutagenic activity in combination with 2-AA in a human body fluid, urine samples of cigarette smokers (2 packs/day) were tested in the Ames assay. Only the mutagenicity of 2-AA was enhanced by smoker's urine extract. Since the brand of cigarettes from which CSC was obtained was different from those smoked by the individuals who provided the urine samples, the results indicated that there is a co-mutagenic factor present in cigarette smoke. (20 Refs)

REVIEWS AND OTHER COMPOUNDS

50. SMOKING AND LUNG CANCER--NOW.

Huhti E
Dept. Medicine, Univ. Central Hosp., SF-90220 Oulu, Finland
Eur J Respir Dis; 62(3):147-149 1981

The relationship between smoking and lung cancer is summarized in the light of r ecent knowledge and suggestions concerning cigarette 'tar'. The tar contains important carcinogens such as benzo(a)pyrene (BP) and its metabolites. BP reactions with human lymphocyte DNA are known, and the smoke-induced DNA damage appears to be correlated with the risk of lung cancer. The tar content of cigarettes sold in the developed countries has decreased since the 1950s, and the carcinogenicity of the tar has been reduced. This explains why male smokers who died in the 1950s had more histologic changes in the bronchial epithelium than those who died in the 1970s. Both low-tar and filter cigarettes may be associated with reduced lung cancer mortality. The least detrimental cigarettes should be those with a medium nicotine yield (1.0-1.2 mg) and a tar content less than 10 mg. (20 Refs)

51. ENDOGENOUS CARCINOGENS.

Hill MJ
Bacterial Metabolism Res. Lab., Central Public Health Lab., London, England
Practitioner; 225(1356):803-804,807-809 1981

Estradiol is a potential endogenous carcinogen. Consuming a high fat/high energy diet, by increasing circulating estrogen levels and estrogen receptor activity, may increase the risk of carcinogenesis in estrogen-dependent tissues (breast, endometrium, possibly ovary). The role of of cholesterol in carcinogenesis is not yet clear. The author's studies showed no relationship between fecal cholesterol levels and the risk of intestinal cancer in case-control studies. Some of the numerous urinary metabolites of tryptophan seem to be related to non-industrial bladder cancer. Intestinal bacteria can derive carcinogenic substances (ethionine, phenol, p-cresol, N-nitroso compounds, bile acid metabolites, etc) from dietary components and convert exogenous chemicals (eg, polycyclic aromatic hydrocarbons) to proximate carcinogens. It is relatively easy to determine which carcinogens might be produced under ideal conditions, but there is limited information on which carcinogens are actually produced in vivo, and very little information regarding their importance. (27 Refs)

52. PCBS, DYES TOP LIST OF PAPER INDUSTRY TOXIC CHEMICAL CONCERNS FOR THE 80'S.

Festa JL
American Paper Inst.
Pulp Pap; 55(7):156-158,162 1981

The important toxic and health issues currently facing the forest products industry are reviewed. A list of major federal legislative authorities under which toxic substances are now being regulated is provided. Issues presented include cost of the proposed polychlorinated biphenyl ban and recent federal regulatory action, the possible link between wood dust and nasal cancer, attention now being focused on dyes derived from benzidine and its congeners and on formaldehyde, and worker safety studies being conducted by the National Institute for Occupational Safety and Health. The major federal requirements for record keeping and reporting on hazardous substances are discussed. (no Refs)

53. FIREFIGHTER EXPOSURE TO ORGANIC CARCINOGENS (MEETING ABSTRACT).

Bendix S
Bendix Environmental Research, Inc., San Francisco, CA
J Occup Med; 23(4):305 1981

Burn, acute cardiac and respiratory hazards have been the past focus of attention to medical problems of firefighters. Firefighters are exposed to complex chemical mixtures of vaporized, off-gassed, decomposed and newly synthesized organic chemicals under conditions where they rarely know what they are breathing or what special chemicals hazards they may encounter. Self-contained breathing apparatus may not be worn, may not be available, or may not be properly maintained to preserve designed function. It is time to look at the long-term consequences of firefighter exposure to vinyl chloride, dioxins, urethane, benzene, tetrachloroethane, polyaromatic hydrocarbons and other carcinogens. Record-keeping and medical follow-up need improvement. (no Refs)

54. THE ELIMINATION OF CARCINOGENIC RISKS IN CONSUMER PRODUCTS.

Preuss PW
Health Sciences, United States Consumer Product Safety Commission, Washington, DC
Ann NY Acad Sci; 363:63-78 1981

Statutes of the Consumer Product Safety Commission (CPSC) designed to assure that marketed products do not cause injury or illness are reviewed. Regulatory techniques include dissemination of product information to the media and consumers, labeling of consumer products, establishing performance or other standards, and banning certain consumer products. On six occasions in its 8 yr of existence, the CPSC has determined that the products contain materials which present a risk of human cancer. Each of the six regulatory actions were unique. The products involved included vinyl chloride, asbestos tris(hydroxymethyl)aminomethane (TRIS), and benzene. Problems associated with balancing the risks, costs, and benefits are reviewed. An appendix containing the CPSC proposed methodology for commission consideration of findings under section 9(c) of the Consumer Product Safety is included. (no Refs)

55. CHEMICAL RADIATION SENSITIZERS AND PROTECTORS: RECENT DEVELOPMENTS.

Kim JH, Chu FCH
No affiliation given
Clin Bull; 11(1):5-11 1981

Findings and prospects with oxic and hypoxic radiosensitizers and with radioprotectors are reviewed. The key radiosensitive site is evidently the the DNA molecule. As oxic radiosensitizers the halogenated pyrimidines, such as 5-chlorodeoxyuridine, 5-bromo-deoxyuridine, and 5-iodo-deoxyuridine, are structural analogues of thymidine. They are incorporated into replicating DNA,resulting in increased sensitivity to irradiation. Clinical applications of the halogenated pyrimidines has been limited, because the sensitivity of normal and tumor tissues is increased equally. Molecular oxygen has the greatest ability of any agent to sensitize cells to radiation. Apparently its interaction with free radicals prevents repair of radiation-induced lesions. Since solid tumor cells are often hypoxic, chemicals that mimic oxygen effects have been tested. These have the advantage of being slowly metabolized. Paranitroacetophenone has sensitizing properties, but also show toxicologic and pharmacological problems. Among the nitroimidazole compounds, metronidazole (5-nitroimidazole) and misonidazole (2-nitroimidazole) have shown promise. The sensitizing effect of these compounds is due to the nitro group, with cytotoxicity and drug solubility due to the side chain. Aminothiols, such as cysteine and cysteamine have the ability to protect against radiation. The most promising of these compounds is WR-2721. (24 Refs)

56. EFFECTS OF METABOLIC INHIBITORS ON CELL LETHALITY AND MUTATION INDUCTION IN CHINESE HAMSTER CELLS. II. THE EFFECT OF POSTTREATMENT WITH NON-TOXIC CONCENTRATIONS OF THYMIDINE.

Brennand J, McMillan S, Fox M
Paterson Lab., Christie Hosp. and Holt Radium Inst., Manchester, M20 9BX, England
Chem Biol Interact; 36(1):89-106 1981

The ability of posttreatment exposure to non-toxic concentrations of thymidine (TdR) to enhance the lethal effects of a number of alkylating agents, x-rays and UV and the lethal and mutagenic effects of N-ethyl-N-nitrosourea (ENU) and N-methyl-N-nitrosourea (MNU) has been examined in V79 cell lines. TdR posttreatment enhanced the cytotoxic effects of ethyl methanesulfonate (EMS), MNU and ENU but not of UV or x-rays and increased both the spontaneous and MNU- and ENU-induced frequencies of azaguanine resistant (AzR) mutants. No significant effect of TdR on the spontaneous frequency of thioguanine resistant (TGR) mutants was demonstrated but the frequency of MNU-induced mutants to TGR was enhanced. The effects on expression of both potentially lethal and premutagenic damage were reversed by addition of an equimolar concentration of deoxycytidine (dCdR). The enhancement in spontaneous and induced mutant frequency (IMF) at the HGPRT locus appears to be due to an alteration in the selective efficiency of purine analogues due to alteration in growth kinetics of cells exposed to TdR or treated with alkylated agents or posttreatment with thymidine after alkylation damage and not to an alteration in the miscoding potential of alkylated bases. (Author abstract) (17 Refs)

57. CARCINOGENIC RISK MANAGEMENT IN THE UNITED STATES.

Selikoff IJ
Environmental Science Lab., Dept. Community Medicine, Mount Sinai Sch. Medicine, City Univ. New York, New York, NY, 10029
Ann NY Acad Sci; 363:283-293 1981

Carcinogenic risk management is in the developmental stage in the United States. Data from studies of smoking, asbestos, and vinyl chloride have shown the effect of carcinogen dose o n the incidence and development of cancers. As a result, the yes-or-no approach to carcinogens has been replaced by regulation based on the dose-response approach. Observation and regulation of carcinogens is being extended from the workers who produce them to include anyone who is exposed during the life of the carcinogens. Other aspects under study include latency, absence of thresholds, dose-induction periods, and multiple factor interactions. The extrapolation of animal data to man remains a debated subject. Observations indicate that, with at least some carcinogens, risk is reduced in time if exposure to the carcinogen ceases. The relationship between mutagenicity and carcinogenicity is still uncertain. The reproductive effects of carcinogens and the decision to ban or control them present ethical and legal questions that remain unanswered. (15 Refs)

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CHEMICAL CARCINOGENESIS

1. THE GENETIC TOXICOLOGY OF ALDRIN AND DIELDRIN.

Ashwood-Smith MJ
Environmental Toxicology Res. Group, Dept. Biology, Univ. Victoria, Victoria, BC V8W 2Y2, Canada
Mutat Res; 86(2):137-154 1981

RADIATION CARCINOGENESIS

2. EFFECTS OF LOW-LEVEL RADIATION ON BIOLOGIC SYSTEMS: A LITERATURE REVIEW.

Best TL, Hoditschek B
Eastern New Mexico Univ., Portales, NM
Effects of Low-Level Radiation on Biologic Systems: A Literature Review. Available from National Technical Information Service, Springfield, VA, as SAND-80-7143:, 246 pp., 1981.

3. PHOTOCARCINOGENESIS: AN OVERVIEW.

Forbes PD
Skin and Cancer Hosp., 3322 North Broad St., Philadelphia, PA, 19140
J Invest Dermatol; 77(1):139-143 1981

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4. EPIDEMIOLOGICAL CORRELATIONS BETWEEN DIET AND CANCER FREQUENCY.

Correa P
Louisiana State Univ. Medical Center, New Orleans, LA, 70112
Cancer Res; 41(9,part2):3685-3689 1981

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Talbot JM
Life Sciences Res. Office, Federation of American Societies for Experimental Biology, Bethesda, MD, 20014
Fed Proc; 40(9):2337-2342 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

6. PRIMARY HEPATIC CANCER IN ALCOHOLICS.

Tamburro CH, Lee HM
Liver Res. Center, Div. Digestive Diseases and Nutrition, Univ. Louisville Health Sciences Center, 511 South Floyd St., Louisville, KY, 40232
Clin Gastroenterol; 10(2):457-477 1981

7. PANCREATIC CANCER AND ALCOHOL.

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Dept. Medicine, Chiba Univ. Sch. Medicine, 1-8-1 Inohana, Chiba City (280), Japan
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Schwartz DA
Inst. Medicine, Far Eastern Univ., Manila, Philippines
Trop Geogr Med; 33(1):1-7 1981

9. GENETICS OF WILMS'S TUMOR.

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Hum Genet; 57(3):231-246 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

10. NEOPLASMS: COMPARATIVE PATHOLOGY OF GROWTH IN ANIMALS, PLANTS, AND MAN.

Kaiser HE
Dept. Pathology, Univ. Maryland Sch. Medicine, Baltimore, MD
Neoplasms: Comparative Pathology of Growth in Animals, Plants, and Man. Baltimore, Williams and Wilkins, 908 pp., 1981.

11. PULMONARY CARCINOGENESIS: ARYL HYDROCARBON HYDROXYLASE.

McLemore TL, Martin RR
Dept. Medicine, Baylor Coll. Medicine, Houston, TX, 77030
Cancer Treat Res; 1:1-34 1981

12. THE GENETIC TOXICITY OF HYDROXYLAMINES.

Marfey P, Robinson E
Dept. Biological Sciences, State Univ. New York at Albany, Albany, NY, 12222
Mutat Res; 86(2):155-191 1981

MODIFICATION OF CARCINOGENESIS

13. MODIFYING FACTORS OF CHEMICAL CARCINOGENESIS.

Beliaev II, Litvinov IuA
Medical Inst., Gorki, USSR
Gig Sanit; (6):59-62 1981
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14. ANTIPROLIFERATIVE EFFECTS OF RETINOIDS RELATED TO THE CELL CYCLE-SPECIFIC INHIBITION OF ORNITHINE DECARBOXYLASE.

Russell DH, Haddox MK
Dept. Pharmacology, Univ. Arizona Coll. Medicine, Tucson, AZ, 85724
Ann NY Acad Sci; 359:281-297 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

15. PATHOGENESIS OF THYMIC LYMPHOMAS IN C57BL MICE.

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Laboratoire d'Anatomie Pathologique, Tour de Pathologie B. 23, Universite de Liege au Sart Tilman, 4000 Liege, Belgium
Pathol Res Pract; 171(2):268-278 1981

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16. CRITICAL ASSESSMENT OF THE VALUE OF IN VITRO CELL TRANSFORMATION FOR PREDICTING IN VIVO CARCINOGENICITY OF CHEMICALS.

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(c/o Lohman, P. H.), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 86(2):233-242 1981

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17. MAMMALIAN GENETICS AND CANCER.

Russell ES
Jackson Lab., Bar Harbor, ME, 04609
Prog Clin Biol Res 45: 327 pp., 1981.

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CHEMICAL CARCINOGENESIS

Miscellaneous Agents

SERIES CK13 No. 82/02

FEBRUARY, 1982

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HYDRAZINES AND RELATED COMPOUNDS

1. ABERRANT METHYLATION OF LIVER DNA IN RATS DURING HEPATOTOXICITY.

Barrows LR, Shank RC
(c/o Shank) Community and Environmental Medicine, Coll. Medicine, Univ. California at Irvine, Irvine, CA, 92717
Toxicol Appl Pharmacol; 60(2):334-345 1981

Aberrant methylation of liver DNA as a response to hydrazine was studied. Male Fischer rats were given hydrazine (60 or 90 mg/kg body wt) by intubation. Liver DNA was analyzed using four high-pressure liquid chromatography methods,

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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a paper chromatography method, and UV absorption spectrometry. Hepatotoxic DNA products were identified as 7-methylguanine (7MG) and O6-methylguanine (O6MG). Administration of [methyl-3H]methionine simultaneously with hydrazine produced labeled 7MG and O6MG, indicating that methylation of DNA was mediated by methionine and S-adenosylmethionine. Aberrant methylation of DNA was also produced by administering ethanol (5 g/kg) or carbon tetrachloride (1 g/kg). Evidently such methylation may be a nonspecific response by the liver to chemical injury. (25 Refs)

2. ON THE PECULIARITIES OF METHYLATION OF DNA OF DIFFERENT TISSUES OF RAT'S FETUS AND MATERNAL ORGANISM AFTER 1,2-DIMETHYLHYDRAZINE TREATMENT.

Likhachev AYa, Petrov AS
N. N. Petrov Res. Inst. Oncology, USSR Ministry Public Health, Leningrad, USSR
Vopr Onkol; 27(7):71-73 1981

A high rate of DNA methylation in the liver and large colon mucosa was registered 6 hr after dimethylhydrazine (SDMH) treatment of rats with 19-day gestations. However, in fetal liver, a low concentration of methylated guanine (7-methyl guanine) derivatives was found, while in large colon and brain, these substances were not detected at all. It is suggested that the resistance of embryonal tissues to the transplacental effect of SDMH is due to the underdeveloped enzymatic system of the fetus. (Author abstract) (8 Refs) (In RUS)

3. ALTERATIONS IN SURFACE ULTRASTRUCTURE AND ANIONIC SITES OF RAT DIMETHYLHYDRAZINE-INDUCED INTESTINAL TUMORS.

Jacobs LR
Dept. Internal Medicine, Sch. Medicine, TB 192, Univ. California, Davis, CA, 95616
Virchows Arch [Cell Pathol]; 37(2):207-216 1981

The relative roles of cell surface shedding and electronegative charge as determinants of metastatic capacity were studied in experimentally produced intestinal tumors. The ultrastructural organization and distribution of anionic sites on the luminal plasma membrane surface components were examined in small intestinal and colonic tumors induced in male Sprague-Dawley rats with 1,2-dimethylhydrazine. The overall distribution of negatively charged groups was demonstrated with ruthenium red staining. Compared to normal epithelial cells, neoplastic cells revealed evidence of decreased cell surface shedding as manifested by decreased numbers of membrane-bound bodies, and an increased quantity of glycocalyx. Malignant cell surfaces were directly exposed to the intestinal lumen as a result of losing the enteric surface coat covering. The exposed microvilli appeared damaged with shortening and blunting. The glycocalyx and surface coat both reacted strongly with ruthenium red indicating the presence of anionic sites. As a result of surface coat loss, the malignant cell surface components revealed an overall decrease in net negative charge. These alterations in cell surface component ultrastructure and electronegative charge appear to be consistent with the low capacity for chemically induced rat intestinal tumors to metastasize. (Author abstract) (15 Refs)

4. UTILIZATION OF BLOOD ANALYSES TO EVALUATE METABOLIC CHANGES IN CONTROL AND 1,2-DIMETHYLHYDRAZINE-TREATED ADULT MALE FISCHER RATS.

Southern JT, Schiller CM
(c/o Schiller) Lab. Organ Function and Toxicology, Natl. Inst. Environmental Health Sciences, P. O. Box 12233, Research Triangle Park, NC, 27709
Cancer Lett; 14(1):47-54 1981

Seven-wk-old male Fischer rats received 1,2-dimethylhydrazine hydrochloride (DMH: 35 mg/kg) by intubation and were examined 1.5 yr later for tumor incidence at which time blood analyses were performed. The incidence of tumors in the treated animals was 78%, while no tumors were seen in controls. Most of the tumors were in the colon. There were statistically significant differences between treated and control animals in total WBC, percentage of lymphocytes, and in the percentage of eosinophils and segmented cells. Treated animals had a lower lymphocyte number and an elevated level of polymorphonuclear WBC. Treated animals had decreases in serum Na and K and increase in phosphate; the ion balance of treated animals was decreased. Serum albumin levels were significantly elevated, total protein levels were lower, SGOT and SGPT levels were decreased and creatine phosphokinase level was elevated in treated animals. The albumin/globulin ratio was increased 3.5-fold in the treated animals. Creatinine concentration was decreased in the treated animals. These data obtained using routine hematoplasia analysis and biochemical analysis with the Sequential Multiple Analyzer Computer Multitest system indicate that the routine clinical analyses as performed with these techniques can be readily adapted to evaluate samples from laboratory animals. (29 Refs)

5. EFFECT OF MAJOR SMALL BOWEL RESECTION ON DIMETHYLHYDRAZINE-INDUCED BOWEL CARCINOGENESIS.

Harte PJ, Steele G, Rayner AA, Munroe AE, King VP, Wilson RE
(c/o Steele) Brigham and Women's Hosp., 75 Francis St., Boston, MA, 021151
J Surg Oncol; 18(1):87-93 1981

We have investigated the effect of distal small bowel resection on chemically induced tumors of the gastrointestinal tract in Wistar/Furth (W/Fu) rats. Dimethylhydrazine (DMH) (20 mg/kg sc once wk x 16) was commenced 3 mo after rats underwent resection of the distal 30 cm of small bowel (1/3 resection) or after sham small bowel resection (controls). Fifty wk after the start of DMH administration, tumors were found in 15 of 25 animals who underwent small bowel resection compared to 9 of 31 animals in the control group (p less than 0.05). After small bowel resection, 8 of 15 tumors occurred at the site of anastomosis but no anastomotic tumors were seen after sham resection. In addition, tumors were larger and more invasive after small bowel resection. These data indicate that major small bowel resection pote ntiates DMH induced-intestinal carcinogenesis. (Author abstract) (28 Refs)

6. MUTAGENICITY OF REACTION PRODUCTS OF SULPYRINE WITH NITRITE.

Sakai A, Yoshikawa K, Tanimura A, Tomita I
Div. Food Additives, Natl. Inst. Hygienic Sciences, Kamiyoga 1-18-1, Setagaya-ku, Tokyo, Japan
Mutat Res; 90(1):57-65 1981

The mutagenicity of three N-nitroso products of sulpyrine (1-diketobutyryl-1-phenyl-2-methyl-2-nitrosohydrazide hydrate

(DPMN), 4-(N-methyl-N-nitroso)aminoantipyrine (MNAA), and 1-acetyl-1-methyl-2-nitroso-2-phenylhydrazine) and of related compounds (4-methylaminoantipyrine, 1-acetyl-1-methyl-2-phenylhydrazine, 4-hydroxyantipyrine, sulpyrine, and sodium nitrite) was tested on Salmonella typhimurium TA100 and TA98. DPMN, MNAA, and sodium nitrite were mutagenic to TA100 but not to TA98. None of the other compounds were mutagenic to either strain. Activation of mutagenicity with rat-liver microsomal preparation (S9 mix) was required by MNAA, but not by DPMN. The addition of L-cysteine or glutathione markedly increased the mutagenicity of DPMN; the enhancing effects were proportional to concentration added. The possibility that sulpyrine might pose a carcinogenic hazard in man is discussed. (25 Refs)

HETEROCYCLIC COMPOUNDS

7. BACTERIAL MUTAGENICITY AND TOXICITY OF CYCLOALIPHATIC EPOXIDES.

Frantz SW, Sinsheimer JE
(c/o Sinsheimer) Coll. Pharmacy, Univ. Michigan, Ann Arbor, MI, 48109
Mutat Res; 90(1):67-78 1981

The Ames mutagenicity test with Salmonella was used to investigate mutagenicity of 12 cycloaliphatic epoxides without the addition of liver homogenate fractions. Eight compounds exhibited base-pair substitution mutagenic activity. Mutagenicity decreased with expanding ring size, while inhibition of bacterial growth increased with increasing ring size. Epoxide toxicity at the doses required for mutagenicity prevented establishment of meaningful dose-response relationships. Petri dish sealing bands were used to prevent loss of volatile compounds during 48 hr incubation. Mutagenicity was greater in TA1535 than in TA100; toxicity was more pronounced in TA100. Toxicity was not reduced by the use of less permeable strains (TA92, TA1950, and TA2410). Cyclooctane oxide testing with TA1975 (repair-proficient) and TA1535 (repair-deficient) demonstrated that the bacteria were not being killed by damage to DNA, since toxicity was not reduced in TA1975. The results confirm that cis-1,2-disubstituted oxiranes are mutagenic. (26 Refs)

8. IN VIVO AND IN VITRO ETHYLENE OXIDE EXPOSURE OF HUMAN LYMPHOCYTES ASSESSED BY CHEMICAL STIMULATION OF UNSCHEDULED DNA SYNTHESIS.

Pero RW, Widegren B, Hogstedt B, Mitelman F
Wallenberg Lab., Univ. Lund, Fack 7031, 220 07 Lund 7, Sweden
Mutat Res; 83(2):271-289 1981

Evidence of toxic exposure to ethylene oxide (EO) in factory workers producing disposable medical equipment was sought in 17 exposed women and 11 unexposed female controls from the same plant. EO exposure was 0.5-1.0 ppb for 40 hr/wk in 12 packers and 5-10 ppb for 8 hr/wk in 4 sterilizers and 1 lab technician, using the measurement of N-acetoxy-2-acetylaminofluorene (NA-AAF)-induced unscheduled DNA synthesis (UDS) in lymphocytes as the assay. The results for the controls in this study agreed with previous results for unexposed subjects: age and/or chromosome aberrations increased in a positive linear manner with increases in NA-AAF-induced UDS. However, the results for the EO-exposed packers were completely different for these two parameters: tendencies toward negative linear correlations were observed that were so divergent from controls (even for this small sample size) that these two groups were shown to be borderline significantly different populations. The data for the other group of exposed workers was nearly significantly different from that for the packers, indicating that perhaps the EO exposure in this group was not high enough to cause a significant reduction in NA-AAF-induced UDS. These results were corroborated by in vitro measurements of EO-induced (0.1-30 milliM) UDS in cultured lymphocytes: at greater than 2 milliM EO, UDS was inhibited, and even at the 0.1 milliM dose where UDS was not affected the exposed cells were sensitized to further exposure to NA-AAF, which caused a 40% cytotoxicity compared with 5% in controls. EO is toxic to lymphocytes and nontoxic doses of EO can sensitize cells to the cytotoxic action of other mutagens. (21 Refs)

9. CHANGES IN ENERGY METABOLISM IN THE GERM CELLS AND EHRLICH ASCITES TUMOR CELLS.

Floridi A, Bellocci M, Paggi MG, Marcante ML, De Martino C
Istituto Regina Elena per lo Studio e la Cura dei Tumori, viale Regina Elena 291, Rome, Italy
Chemotherapy; 27(Suppl2):50-60 1981

Experiments were carried out to assess whether the mitochondrial changes induced by 1-p-chlorobenzyl-1H-indazole-3-carboxylic acid (AF 1312/TS) in rat seminiferous tubules are due to a direct action of the drug on germ cell organelles or whether they are mediated by a functional impairment of the Sertoli cells, whose cytoplasm is observed to undergo vacuolization. Control germ cell had a high respiration rate (measured as oxygen consumption) and low level of anaerobic glycolysis, indicative of mainly oxidative energy metabolism; treatment of germ cells with AF 1312/TS caused a 38% decrease in oxygen consumption, a doubling of aerobic glycolysis, no effect on anaerobic glycolysis, and an 80% reduction in the Pasteur effect, suggesting a direct action by the drug on the cell rather than an indirect action via decreased cell survival. Treatment with AT 1312/TS did not modify the ADP/O ratio but caused a marked reduction in the respiratory control ratio, indicating an effect on the mitochondria. The respiratory rate as a function of ADP concentration (the ADP affinity) was essentially the same for control and treated mitochondria at the highest ADP concentrations (150 uM), indicating that the drug is not an uncoupler but acts to modify the ADP control mechanism; but at the lowest ADP concentrations, the respiratory rate was markedly lower in the mitochondria of treated rats, indicating the drug's effect on ADP affinity. A related compound, lonidamine, had similar effects in germ cells and isolated germ-cell mitochondria. Both drugs also exerted these effects in Ehrlich ascites tumor cells but did not affect isolated liver mitochondria. The class of compounds represented by these two drugs appears to affect preferentially the mitochondria of germ cells and tumor cells; other evidence suggests that it is the mitochondrial hexokinase system that is affected. (5 Refs)

INORGANIC AGENTS AND PARTICULATES INCLUDING FIBERS

10. ONCOGENIC TRANSFORMATION AND CELL LYSIS IN C3H/10T1/2 CELLS AND INCREASED SISTER CHROMATID EXCHANGE IN HUMAN LYMPHOCYTES BY NICKEL SUBSULFIDE.

Saxholm HJ, Reith A, Brogger A
Inst. Pathology, Univ. Oslo, Rikshosptalet, National Hosp., Oslo, Norway
Cancer Res; 41(10):4136-4139 1981

We have scored frequency of transformation and appearance of the oncogenic marker 'long microvilli' in mouse embryo fibroblast C3H/10T1/2 cells in culture for the compound Ni3S2. Furthermore, we have scored for Ni3S2-induced sister chromatid exchange in cultured human lymphocytes. Nickel subsulfide in moderate doses caused morphological transformation to Type I, II, and III foci and induced long microvilli on the cells in the transformed cultures, demonstrating oncogenic transforming ability. Higher doses led to cell lysis after a lag period. The carcinogenic potency of Ni3S2 in this system was not as strong as that of methylcholanthrene. Ni3S2 increased the sister chromatid exchange frequency in human lymphocytes in a marginal, not dose-dependent way. The increased sister chromatid exchange may indicate that the carcinogenic effect of Ni3S2 is genetic rather than epigenetic. (Author abstract) (39 Refs)

11. CARCINOGENICITY, MUTAGENICITY AND TERATOGENICITY OF NICKEL.

Leonard A, Gerber GB, Jacquet P
Dept. Radiation Biology, C.E.N.-S.C.K., B-2400 Mol, Belgium
Mutat Res; 87(1):1-15 1981

Nickel is widely used in the metallurgical industry. It is not released into the environment in large quantities, but poses an occupational hazard to human health. Ingested nickel is not readily absorbed, hence it is relatively nontoxic. Inhaled nickel is toxic in certain forms. Nickel carbonyl at 30 ppm for 30 min is lethal. Half-life in the body is less than 1 wk. Metallic nickel can cause sensitization of the immune system. Nickel compounds are carcinogenic in inverse proportion to their solubility in aqueous media. Nickel sulfide appears to have the greatest carcinogenicity. The lungs and nasal tissue are favored sites of nickel-induced cancers. Tumor types induced include undifferentiated sarcoma, fibrosarcoma, carcinoma, leukemia, and lymphoma. The mutagenicity of nickel is uncertain: nickel may be mutagenic in mammals but not in microorganisms. It is capable of crossing the placenta and has teratogenic effects, including fetal mortality, exencephaly, and cystic lung disease, in some species. Effects may be delayed by retarded transfer across the placenta. (129 Refs)

12. FACTORS INFLUENCING THE PHAGOCYTOSIS, NEOPLASTIC TRANSFORMATION, AND CYTOTOXICITY OF PARTICULATE NICKEL COMPOUNDS IN TISSUE CULTURE SYSTEMS.

Costa M, Abbracchio MP, Simmons-Hansen J
Div. Toxicology, Dept. Pharmacology, Univ. Texas, Medical Sch. at Houston, P.O. Box 20708, Houston, TX, 77025
Toxicol Appl Pharmacol; 60(2):313-323 1981

Chinese hamster ovary (CHO) cells were exposed in vitro to crystalline nickel compounds (alpha-Ni3S2, alpha-NiS, and Ni3Se2) or non-crystalline nickel compounds (amorphous NiS, metallic nickel, Ni3O2, or NiO). The CHO cells actively phagocytized the crystalline compounds but not the non-crystalline compounds. In cultured Syrian hamster embryo (SHE) cells, the crystalline compounds showed high cellular transformation activity, while the non-crystalline compounds showed only weak transformation activity. Water-soluble NiCl2 showed about 30% of the transformation activity of alpha-Ni3S2. Particle size had a significant effect on phagocytosis of crystalline nickel compounds. Particles up to 4 micron (um) in diameter were actively phagocytized. Particles above 5 um were not actively phagocytized. Those between 4 and 5 um were phagocytized at a low rate. Ni3S2 phagocytosis was inhibited by the presence of Mn dust, Mn++ ions, dansylcadaverine, actinomycin D, cycloheximide, or amorphous NiS. Mn dust added with crystalline Ni3S2 inhibited induction of morphological transformation due to Ni3S2 in SHE cells. Since particles that were not phagocytized had an inhibitory effect, their actions were evidently extracellular. Crystalline particles, once inside a cell, are then activated as carcinogens by cellular actions that allow transport of the activated forms into the nucleus. (21 Refs)

13. CYTOTOXIC AND CLASTOGENIC EFFECTS OF SOLUBLE AND INSOLUBLE COMPOUNDS CONTAINING HEXAVALENT AND TRIVALENT CHROMIUM.

Levis AG, Majone F
Inst. Animal Biology, Univ. Padua, Padua, Italy
Br J Cancer; 44(2):219-235 1981

Cr(III) and Cr(VI) compounds of varying solubilities have been tested in vitro for their ability to inhibit cell growth and nucleic acid and protein syntheses in BHK cells, to induce alterations in the mitotic cycle in HEp cells, and to increase the frequency of chromosomal aberrations and sister chromatid exchanges (SCE) in CHO cells. All Cr(VI) compounds, and particularly those containing soluble Cr(VI), such as potassium dichromate and zinc yellow, differentially inhibit macromolecular syntheses in BHK cells, that of DNA being always the most affected. Among Cr(III) compounds, which generally have very low cytotoxicity, chromite is particularly active, and inhibits cell growth and DNA synthesis even more than the poorly soluble Cr(VI) compounds. Preincubation in growth medium, with or without metabolizing cell cultures, solubilizes considerable amounts of Cr(VI) from zinc yellow and chromite, but significant amounts are also obtained from the most insoluble Cr(VI) pigments. When BHK cells are treated with such preincubated solns, reduction of soluble Cr(VI) to Cr(III) by cell metabolites is seen with all Cr(VI) compounds, accompanied by decreased cytotoxicity. The same differences between Cr(VI) and Cr(III) compounds apply to the cytotoxic effects on mitosis of HEp cells and the clastogenic effects on CHO cells. The activity of chromite, the only Cr(III) pigment capable of significantly increasing the frequency of SCE, is due to contamination with soluble Cr(VI). In contrast to the very low cytotoxicity of Cr(III), much higher chromium levels are detected in the cells incubated with soluble Cr(III) than with the same concentrations of soluble Cr(VI). 50% and 75% of chromium accumulated in the cells during treatments with Cr(VI) and Cr(III) respectively remains firmly bound to the cells, even when they are incubated for up to 48 hr in normal growth medium. Chromium accumulated in the cells after treatment with Cr(III) is most probably bound to the cell membrane, whereas some of the Cr(VI) is transported through the cell membrane and reduced in the cell nucleus. The results of the present investigation are in agreement with those obtained with the same Cr(VI) and Cr(III) compounds in mutagenicity assays in bacteria and carcinogenicity tests in rodents. A re-evaluation of the mechanisms of chromium carcinogenesis is proposed. (Author abstract) (54 Refs)

14. DNA-PROTEIN CROSS-LINKING BY CHROMIUM SALTS.

Fornace AJ, Seres DS, Lechner JF, Harris CC
Lab. Experimental Pathology, Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD, 20205
Chem Biol Interact; 36(3):345-354 1981

DNA-protein cross-links were detected in several types of mammalian cells in culture when they were exposed to chromate salts. The cell types included human bronchial epithelial cells - the apparent cell type of origin of the malignancies reported in chromate workers. The level of cross-linking was proportional to the concentration of chromate used. These cross-links appeared to be persistent since no removal was seen after 12 hr of repair incubation. A low level of DNA single strand breaks (SSB) were also induced after exposure of the cells to chromate but were rejoined after 4 hr of repair incubation. The active form of chromium appears to be the trivalent since chromic but not chromate salts induced DNA-protein cross-links in isolated nuclei. Chromic salts also produced cross-linking between DNA and protein in soln while the hexavalent form was inactive. These data imply that chromate crosses the cell membrane, is reduced to the trivalent form and induces stable linkages of DNA to protein. (Author abstract) (19 Refs)

15. THE CARCINOGEN ASSESSMENT GROUP'S FINAL RISK ASSESSMENT ON ARSENIC.

Environmental Protection Agency
Environmental Protection Agency, Washington, DC
The Carcinogen Assessment Group's Final Risk Assessment on Arsenic. Available from National Technical Information Service, Springfield, VA, as PB81-206013:, 34 pp., 1981.

An estimate of the potential cancer hazard to populations exposed to airborne arsenic is given. Data analyzed are from occupational studies, estimates of ambient exposure and the number of cancer cases induced in the general or 'non-industrial' exposed populations. Using a linear model and data from three studies (Pinto et al (1977), Ott et al. (1974), and Lee and Fraumeni (1969)), it is estimated that the increase in the lung cancer rate per increase of 1 ug/cu m of atmospheric arsenic was 9.4%, 17.0% and 3.3% respectively, with a geometric mean of these values calculated to be 8.1%. Using this value and data from a revised 1979 Stanford Research Institute arsenic exposure assessment, lifetime risk of respiratory cancer to those near cotton gins is calculated to be as high as 0.0134 and higher than 0.00001 for about 2.81 million people due to all sources of air arsenic exposure. Total atmospheric arsenic caused deaths due to respiratory cancer is estimated to be within a 95% confidence interval of 19.4 to 1.2 deaths annually. (Author abstract)

16. ASBESTOS EXPOSURE IN THE MONFALCONE AREA. A SOCIAL AND PATHOLOGICAL STUDY OF 100 AUTOPSY CASES.

Bianchi C, Brollo A, Miniussi C, Bittesini L
Servizio di Antomia e Istologia Patologica, Ospedale Generale Provinciale, Via Rossini 1, 34074 Monfalcone, Italia
Tumori; 67(4):279-282 1981

Monfalcone is a coastal town with important shipyards. In the present investigation hyaline pleural plaques, lung asbestos bodies, and occupational history were studied in 100 consecutive autopsy cases, collected at the hospital of Monfalcone. Pleural plaques were observed in 72% of males and in 33% of females. Asbestos bodies were found after chemical digestion of pulmonary tissue in 94 cases, and an approx estimation of their amount showed high or very high numbers in 39 cases. Occupational history, obtained from patients' relatives, was suggestive of occupational asbestos exposure in 60 cases, with 37 subjects having worked in the shipyards. Thirteen other patients had had a probable domestic exposure to asbestos. The severity of asbestos exposure in the Monfalcone area is emphasized. (Author abstract) (14 Refs)

17. THE CHEMICAL AND BIOCHEMICAL CHARACTERIZATION OF PARTICULATE MATTER AS PART OF AN EPIDEMIOLOGICAL CANCER STUDY.

Wesolowski JJ, Flessel CP, Twiss S, Cheng J, Chan R, Garcia L, Ondo J, Fong A, Lum S

Air and Industrial Hygiene Lab., California Dept. Health Services, Berkeley, CA, 94704

J Aerosol Sci; 12(3):208-212 1981

During the winter season (November-February) 6-day high-vol glass filters were composited from each of 15 stations in Contra Costa County, California. Particulate matter was analyzed for total suspended particulate, benzene soluble organics (BSO), SO4, NO3, Pb, selected polycyclic aromatic hydrocarbons (PAH), and mutagenic activity. The five PAH, benzo(a)pyrene, benzo(ghi)perylene, benz(a)anthracene, chrysene, and coronene [a possible tracer for vehicle emissions], were quantitated by UV absorption an fluorescence. Mutagenicity was determined using the Ames test, with and without rat liver fraction S9. Since the correlation coefficients (Spearman) between mutagenicity (+S9) values and concentrations of the various PAH were only 0.33, 0.41, 0.36, 0.31 and 0.51, respectively, it is concluded that quantitation of the five PAH is not a good measure of air mutagenicity, which is consistent with the fact that these PAH constitute only about 2% of total air mutagenicity Contour maps showing variations in air pollution will be useful for comparison of cancer incidence. The monitoring stations do provide some data on sources of pollution. High correlations between Pb, BSO and the five PAH implicate vehicles as a source. However, low correlations between mutagenicity (with or without S9) and these factors indicate mutagenicity may also derive from other sources. (12 Refs)

18. ASBESTOS, AN ENVIRONMENTAL POLLUTANT.

Zamfir G, Diaconu R

Institutul de igiena si sanatate publica, Iasi, Romania

Igiena; 30(1):1-9 1981

Studies on the carcinogenic effect of asbestos are reviewed. One hundred and eighty-nine cases of cancer were found among 623 workers exposed to asbestos for more than 20 yr in New York and New Jersey against an expected mortality of 47.2. Lung cancer was found in 84 cases, pleural mesothelioma in 8, peritoneal mesothelioma in 24, cancer of the stomach, colon, rectum, and esophagus in 41, and cancer of other localizations in 32. Positive correlation was found between digestive tract cancer mortality and the product of exposure. There is no conclusive evidence of increased incidence of pleural and peritoneal mesothelioma due to ingestion of drinking-water containing asbestos. (39 Refs) (In RUM)

AMIDES, CARBAMATES AND UREAS

19. MUTAGENICITY OF AMIDE TYPE AND CARBAMATE TYPE DIAZOALKANE-GENERATING AGENTS IN SALMONELLA/MICROSOME ASSAY.

Morita T, Sawaki M, Mifuchi I
Shizuoka Coll. Pharmacy, 2-2-1 Oshika, Shizuoka, 422, Japan
Chem Pharm Bull (Tokyo); 29(6):1758-1762 1981

Both amide type and carbamate type N-nitroso compounds, which have a common structure and have been reported to be excellent diazoalkane-generating compounds were examined for mutagenicity by measuring their ability to create histidine (his) prototrophic revertants of two his-dependent Salmonella typhimurium strains: T100 (a base-pair substitution strain) and TA98 (a frameshift strain), with and without metabolic activation by S-9 mix. Six compounds of each type having systematic substitutions at two different sites of the basic common structure were examined systematically over dose ranges of 0.27-2.7 umole (4 x 10(-5) to 4 x 10(-2) M). In the absence of activation, none of the amide type compounds showed any mutagenicity in either strain. With metabolic activation, two of six amide type compounds (both having a benzyl group in the same position) were weakly mutagenic to TA100. In the absence of S-9 mix, only one of six carbamate type compounds showed any mutagenicity (against TA98); in the presence of S-9 mix, all six carbamate compounds were mutagenic against TA100 over a wide range of concentrations and two of six were weakly mutagenic against TA98. There is apparently a structure-mutagenicity relationship for amide type and carbamate type compounds that is principally dependent upon the rate of chemical generation of diazoalkane or phenyldiazomethane in alkaline soln. (8 Refs)

AMINO ACID ANALOGS AND MODIFIED NUCLEIC ACID CONSTITUENTS

20. BIOLOGICAL ACTIVITIES AND MODES OF ACTION OF 9-ALPHA-D-ARABINOFURANOSYLADENINE AND 9-ALPHA-D-ARABINOFURANOSYL-8-AZAADENINE.

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Biochem Pharmacol; 30(16):2325-2332 1981

From earlier studies it is known that 9-alpha-D-arabinofuranosyladenine (alpha-araA) and 9-alpha-D-arabinofuranosyl-8-azaadenine (alpha-ara-8-azaA) have in vitro antiviral activity, are cytotoxic, and are metabolized in mammalian cells to the triphosphates. This study was designed to compare the in vivo antiviral activities of these compounds and their loci of action with those of 9-beta-D-arabinofuranosyladenine (beta-araA). The latter compound selectively inhibits DNA synthesis in intact cells, and its triphosphate is a known inhibitor of DNA polymerases and ribonucleotide reductase. Whereas beta-araA was significantly effective in the treatment of systemic herpes simplex virus Type 1 (HSV-1) infections in mice, alpha-araA and alpha-ara-8-azaA were therapeutically ineffective. Alpha-AraATP at a concentration of approx 1 mM did not inhibit (1) DNA polymerases present in crude extracts of cultured HEp-2 cells; (2) DNA polymerases present in extracts of KB cells; (3) partially purified DNA polymerase-alpha from mouse embryo cells; or (4) DNA polymerases induced by HSV-1 and HSV-2. DNA polymerase-beta from mouse embryo cells was inhibited to a small extent by 10(-4) M alpha-araATP. In contrast, all of these enzymes were inhibited by beta-araATP at a concentration of 10(-5) M (as shown in these or in earlier studies). The reductions of CDP and UDP by ribonucleotide reductase from L1210 cells were not inhibited by alpha-araATP (approx 10(-3) M), whereas beta-araATP produced 70-80% inhibition at this concentration. In cultured HEp-2 cells, alpha-ara-8-azaA inhibited the incorporation of thymidine, uridine, and formate into macromolecules, but it was without effect on the incorporation of adenine and hypoxanthine, and produced marginal inhibition of the incorporation of leucine. alpha-Ara-8-azaA produced a dose-dependent inhibition of the accumulation of [14C]formyl-glycinamide ribonucleotide in HEp-2 cells treated with azaserine and [14C]formate. These results indicate that the alpha-nucleosides inhibit nucleic acid synthesis by mechanisms different from those of beta-ara-A. (Author abstract) (32 Refs)

21. DIFFERENTIAL SENSITIVITY OF NORMAL AND CHEMICALLY TRANSFORMED EPITHELIAL CELLS TO CHOLERA TOXIN.

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Cancer Res; 41(10):4075-4079 1981

We have been studying the regulation of growth by cyclic AMP and other factors in untransformed (K16) and chemically transformed (W8) rat liver epithelial cells. Initially, we found that 8-bromocyclic adenosine 3':5'-monophosphate was a more potent inhibitor of cell replication in K16 than in W8 cells. In addition, the phosphodiesterase inhibitor 1-methyl-3-isobutylxanthine (MIX) caused marked growth inhibition in K16 but not in W8 cells. Through the use of cholera toxin (CT) with or without MIX, we elevated intracellular cyclic AMP levels in a quantifiable fashion. With CT alone or combined with MIX, we observed a dose-dependent morphological change in W8 cells, which consisted of extensive 'process' formation. K16 morphology was not altered at any concentration of CT +- MIX tested. K16 cell growth was only marginally inhibited by CT alone, but markedly inhibited by CT plus MIX. W8 cell growth was moderately inhibited by CT alone or combined with MIX. Analysis of cyclic AMP levels revealed that, at all concentrations of CT +- MIX and at all time periods tested, W8 cells produced significantly more cyclic AMP than K16 cells. It appears that morphological changes and growth inhibition are not necessarily linked and that MIX may inhibit K16 cell replication by means other than its ability to increase intracellular cyclic AMP levels. (Author abstract) (23 Refs)

22. PROMOTION BY UNSATURATED FAT OF AZASERINE-INDUCED PANCREATIC CARCINOGENESIS IN THE RAT.

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Cancer Res; 41(10):3961-3966 1981

Diet has been shown to modulate the incidence of a wide variety of chemically induced cancers in animals. Various diets fed either during the initiation stage or the postinitiation (promotion) stage of carcinogenesis were evaluated for their ability to modulate the incidence of pancreatic cancer. Male Wistar/Lewis rats were treated with multiple injections of the pancreatic carcinogen, azaserine, during a 6-to 7-wk-long initiation phase and were autopsied after a postinitiation phase of 34 or

44 wk. The following diets were evaluated for their effects on the incidence of pancreatic neoplasms during each stage of carcinogenesis: high saturated fat; two high unsaturated fats (corn oil and safflower oil); low protein; and caloric restricted. A purified control diet was fed during that stage when the test diets were not fed. The incidence of pancreatic adenomas and adenocarcinomas was evaluated by light microscopy. Feeding of the caloric-restricted diet during the initiation phase suppressed the pancreatic neoplasm incidence. None of the other diets tested had an effect on the incidence of pancreatic cancer during the initiation phase. During the postinitiation phase, both high-unsaturated-fat diets but not the high-saturated-fat diet significantly elevated the pancreatic neoplasm incidence. The low-protein and caloric-restricted diets had no effect on the neoplasm incidence when fed during the postinitiation phase. Thus, diets high in unsaturated fat appear to promote pancreatic carcinogenesis in the azaserine-treated rat while a diet high in saturated fat failed to show a similar degree of enhancement of pancreatic carcinogenesis. (Author abstract) (42 Refs)

ALIPHATIC HALOGEN COMPOUNDS

23. A PROCEDURE FOR THE QUANTITATIVE MEASUREMENT OF THE MUTAGENICITY OF VOLATILE LIQUIDS IN THE AMES SALMONELLA/ MICROSOME ASSAY.

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Mutat Res; 90(1):31-48 1981

Development and application of an apparatus which allows quantitative study of the distribution and mutagenicity of volatile test chemicals is reported. The containment system is made of materials which are chemically inert with respect to halogenated hydrocarbons. Containment properties of the system were examined using 14C-1,2-dibromoethane and gas liquid chromatographic analysis; 95% of the chemical remained after 48 hr incubation at 37 C. Only two significant solvent compartments were found (the vapor and aqueous phases); use of plastic plates significantly perturbed solvent distribution within the container. Using the Ames Salmonella assay with strains TA1535, TA1537, TA98, and TA100, 10 common haloalkane solvents were tested in the system. Of the 10 compounds, only 1,2-dibromoethane and 1-bromo-2-chloroethane gave positive responses in the standard plate incorporation test; their potencies were approx 1/20-1/50 that determined in the closed system. In the closed system 7/10 compounds exhibited some degree of activity. Mutagenic potencies ranged between 0.001 (1,2-dichloroethane) and 0.172 revertants/nanomole (1,2-dibromoethane). The closed system reduces solvent exposure of personnel and the chance of false positives due to mutagenic impurities. It may provide better simulation of actual (vapor phase) exposure. (27 Refs)

24. CHLOROETHANES: THEIR METABOLISM BY HEPATIC CYTOCHROME P-450 IN VITRO.

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Carcinogenesis; 2(8):697-702 1981

Hepatic Microsomes were obtained from male Long-Evans rats. Microsome suspensions were exposed to 1,1,1-trichloroethane (111T), 1,1,2-trichloroethane (112T), or 1,1,2,2-tetrachloroethane (1122T). Levels of cytochrome P450 were measured, and metabolites of the chloroethanes were identified and quantified. The binding of chloroethanes was enhanced by the induction of cytochrome P-450 by phenobarbital (PB). It was not enhanced by the induction of cytochrome P-448 by betanaphthoflavone (BNF). All three chloroethanes stimulated CO-inhibitable NADPH oxidation (CINO) by the hepatic microsomes. BNF induction decreased CINO for all three chloroethanes. PB induction increased CINO for 111T and 112T, but not for 1122T. CINO and metabolite formation were inhibited by CO, 2-diethylaminoethyl-2,2-diphenylvalerate (SKF-525A), and/or metyrapone. The results confirmed that all three chloroethanes were metabolized by cytochrome P-450. The metabolites of 111T, 112T, and 1122T were 2,2,2-trichloroethanol, monochloroacetate, and dichloroacetate, respectively. Proposed mechanisms for metabolism are described, with relationship to the relative mutagenicity and carcinogenicity of the three chloroethanes. (29 Refs)

25. FAILURE TO DISCRIMINATE INITIATION FROM PROMOTION OF LIVER TUMORS IN A LONG-TERM STUDY WITH THE PHENOBARBITAL-TYPE INDUCER ALPHA-HEXACHLOROCYCLOHEXANE AND THE ROLE OF SUSTAINED STIMULATION OF HEPATIC GROWTH AND MONOOXYGENASES.

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Cancer Res; 41(10):4140-4146 1981

The compound alpha-hexachlorocyclohexane (alpha-HCH) was administered po to female Wistar rats for periods of up to 33 mo; doses were 20 mg/kg/day, 200 mg/kg every 2nd wk, or 420 mg/kg every 3rd wk. Increases of liver size, DNA, RNA, and protein (by 50 to 100%) and of drug-metabolizing enzyme activities (up to 300%) observed previously after single doses of alpha-HCH were found to persist after approx 1/3, 1, and 2 yr of treatment. At 1 and 2 yr, DNA synthesis was measured by [3H]thymidine uptake and was no higher than in controls. All changes regressed upon withdrawal of alpha-HCH after 1 yr of treatment. These findings provide no evidence to suggest a protracted development of toxicity or of growth autonomy in the majority of liver cells. Foci of altered cells, neoplastic nodules, and in 2 animals hepatocellular carcinoma were detected histologically in the livers of 24 of 34 treated rats. In livers of 10 of 22 untreated control rats, foci of altered cells developed 'spontaneously' between 12 and 34.5 mo. If neoplastic lesions were induced by a single dose of diethylnitrosamine, 75 or 150 mg/kg, subsequent treatment with alpha-HCH led to the appearance of hepatocellular carcinoma within 7 mo. Altogether, hepatocellular carcinomas were found in 18 of 21 rats treated with both agents but in only 3 of 26 animals treated with diethylnitrosamine alone. The results show that determination of tumor numbers alone in a long-term animal experiment does not allow one to decide whether alpha-HCH (and similar 'xenobiotic inducers') is an initiating carcinogen or merely promotes tumorigenesis from 'spontaneous' lesions. Our findings support the latter possibility by the failure to detect evidence suggesting initiating potential of alpha-HCH, by the enhanced mitotic response to alpha-HCH in foci of altered cells as reported elsewhere, and by the observation of a permanent stimulatory action on liver growth during prolonged exposure to alpha-HCH. (Author abstract) (46 Refs)

POLYHALOGENATED RING COMPOUNDS INCLUDING INSECTICIDES

26. CARCINOGENIC POTENTIAL OF ROTENONE: SUBCHRONIC ORAL AND PERITONEAL ADMINISTRATION TO RATS AND CHRONIC DIETARY ADMINISTRATION TO SYRIAN GOLDEN HAMSTERS.

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Carcinogenic Potential of Rotenone: Subchronic Oral and Peritoneal Administration to Rats and Chronic Dietary Administration to Syrian Golden Hamsters. Available from National Technical Information Service, Springfield, VA as PB81-190936, 47 pp., 1981.

Three long-term studies were performed to evaluate the carcinogenic potential of the pesticide rotenone in hamsters and rats. Rotenone was administered po to Wistar rats and by ip injection to Sprague-Dawley rats, which were maintained and observed for 14 and 18 mo, respectively. Syrian golden hamsters were maintained for 18 mo on diets containing rotenone in concentrations up to 1,000 ppm. Following these studies the animals were subjected to extensive necropsy. No evidence of an increased incidence of mammary or any other type of neoplasm was noted in the two rat studies. At all dosage levels in the hamster dietary study, no gross or histopathological evidence was obtained to suggest that rotenone induced the formation of mammary tumors. Three adrenal cortical carcinomas were observed in 65 hamsters from the highest dosage group; while suspicious, it is questionable that this occurrence was related to rotenone treatment. There were no other indications of neoplastic events. In ancillary studies there was preliminary evidence that rotenone at levels of 500 ppm in the maternal diet was embryo-toxic and resulted in cannibalism of the young by the maternal animals. A level of 1,000 ppm led to sterility in one or both sexes. Hamsters fed rotenone displayed reduced feed consumption and diminished wt gains during the first few mo of administration. (Author abstract)

27. THE ROLE OF TOXICITY IN THE CARCINOGENICITY OF ENDOSULFAN.

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Sci Total Environ; 20(1):23-47 1981

Two NCI studies examined toxicity and carcinogenicity of endosulfan (ES; 6,7,8,9,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9, methano-2,4,3-benzodioxathiepin-3-oxide; Thiodan) in groups of Osborne Mendel rats and B6C3F1 mice. Male rats initially received 281 or 562 ppm of ES in the diet; females received 89 or 178 ppm. The doses were adjusted upwards to av 408 or 952 ppm (males) and 223 or 445 (females) during the 105-106 wk period of observation. Over a 92 wk span, male mice ingested 3.5 or 6.9 ppm of ES and females ingested 2 or 3.9 ppm. In rats ES significantly increased mortality. Both male and female rats developed lymphosarcoma and benign and malignant neoplasms at all sites; male rats showed high incidence of endocrine neoplasms while females exhibited high incidence of neoplasms of the reproductive system. Chronic interstitial fibrosis was the cause of death in most male rats on either dose. Lesions of the parathyroid gland were related to renal disease. Osteitis fibrosis was found in many male but few female rats. In the mice, ES favored survival compared to controls. In female mice, carcinomas of the liver were found in 6/17 mice on the low dose of ES compared to 1/17 controls. While male mice did not show increased incidence of neoplasms, they developed amyloidosis and chronic inflammation of the kidney. A review includes every known study on carcinogenicity of ES in animals. (35 Refs)

BENZENE DERIVATIVES

28. EFFECTS OF 2-AND 3-TERT-BUTYL-4-HYDROXYANISOLE ON GLUTATHIONE S-TRANSFERASE AND EPOXIDE HYDROLASE ACTIVITIES AND SULFHYDRYL LEVELS IN LIVER AND FORESTOMACH OF MICE.

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Cancer Res; 41(10):3940-3943 1981

Butylated hydroxyanisole, a food additive, has been found to inhibit the neoplastic effects of a wide variety of chemical carcinogens. The commercially available preparations of butylated hy droxyanisole contain two isomers, 2-tert-butyl-4-hydroxyanisole (2-BHA) and 3-tert-butyl-4-hydroxyanisole (3-BHA). Both isomers induce increased activities of glutathione (GSH) S-transferase and epoxide hydrolase and increase acid-soluble sulfhydryl concentration in hepatic and forestomach tissues of A/HeJ mice. The inductions were assayed after 2 wk of feeding diets containing the two isomers. 3-BHA induced an increase in the activity of hepatic microsomal epoxide hydrolase by 1.4x that of the control. The activity of cytosol GSH S-transferase was enhanced by both isomers. In the liver, the 3-BHA induction was more than 3x higher than that of 2-BHA. In the forestomach, however, the induction effect of the two isomers was reversed. The overall magnitude of the induction was much lower in the forestomach than in the liver. Synergistic effects on the induction of GSH S-transferase activity were observed in the forestomach cytosol when mixtures of different proportions of the two isomers were added to the diet. Max enzyme activity was obtained at a ratio of 75% 2-BHA and 25% 3-BHA. No synergistic effect was observed with the corresponding hepatic cytosolic enzyme. The relative inductive effects of 2-and 3-BHA on the acid-soluble sulfhydryl level of liver and forestomach tissues followed closely those on GSH S-transferase activity. The results of the present study show that the two isomers of butylated hydroxyanisole differ in the magnitude of their effects on carcinogen-metabolizing systems of the liver and forestomach. (Author abstract) (27 Refs)

29. ENHANCEMENT OF TUMOR FORMATION IN MOUSE LUNG BY DIETARY BUTYLATED HYDROXYTOLUENE.

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Toxicology; 21(2):95-104 1981

The effect of three antioxidants, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), and ethoxyquin (EQ) on the incidence of urethan-induced lung tumors in male A/J mice was investigated. The test diet containing 0.75% BHT, 0.75% BHA, or 0.75% EQ was given 1 day/wk for 8 wk beginning 1 wk after a single ip injection of urethan (500 or 250 mg/kg body wt).When sacrificed 4 mo after urethan treatment, the BHT-treated mice had a significantly higher multiplicity of tumors (p less than 0.05) than did the animals given urethan alone or urethan followed by BHA or EQ, at both urethan concentrations. A positive control group given 500 mg/kg urethan followed 1 wk later by ip injections of 300 mg/kg BHT in corn oil 1 x/wk for 8 wk had a tumor incidence comparable to that induced by urethan and po BHT, showing that route of administration of BHT is irrelevant with regard to tumor enhancement. When test diet containing 0.75% BHT or 0.75% BHA was given continuously for 8 wk immediately following a single ip injection of 500 or 250 mg/kg urethan and the animals were sacrificed 4 mo after urethan treatment, the BHT-treated mice again had a significantly higher multiplicity of tumors (p less than 0.05) compared with animals given urethan alone or urethan and BHA. When test animals were fed ad libitum for 2 wk such that they ingested an av of 180 mg BHT or 187 mg BHA, then injected with 1,000 mg/kg urethan and sacrificed 4 mo later, the tumor incidence in the BHT-treated animals was similar to that in controls, while BHA pretreatment significantly reduced (p less than 0.05) the tumor incidence. Histologic classification showed that BHT treatment did not alter the types or ratios of tumors induced by urethan. It appears that the use of BHT as a food additive should be reevaluated. (18 Refs)

30. THE DETECTION OF IN VIVO HEMATOTOXICITY OF BENZENE BY IN VITRO LIQUID BONE MARROW CULTURES.

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Toxicol Appl Pharmacol; 60(2):346-353 1981

The hematotoxicity and possible leukemogenicity of benzene was tested. by inhalation was tested in female C57BL/6J mice. Groups of mice were exposed either to normal air or to air containing benzene (400 ppm) for 6 hr/day/5 days/wk for 9 days or 11 consecutive days. Cultures were then made from bone marrow samples. Each culture contained an adherent (A) fraction (consisting of phagocytic mononuclear cells, fat cells, endothelial cells , and epithelial cells) and a non-adherent (NA) fraction (consisting mainly of granulocytes and macrophages). The number of spleen colony-forming cells was progressively reduced in cells from benzene-treated mice. Cultures from benzene-treated mice had a reduced capacity to maintain stem cell proliferation compared to cell cultures from normal cells, as shown by combining normal or treated A fractions with various reinoculations. Evidently benzene injures stem cells, reducing their ability to self-replicate and deranging the A cell population. Neonatal C57BL/6J mice injected with cells from benzene-treated mice did not develop leukemia during 8 mo after injection. This suggests that benzene may promote, rather than initiate, leukemia. (28 Refs)

31. BENZENE AS A RISK FACTOR.

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Arch Geschwulstforsch; 51(7):575-578 1981

Exposure to benzene as a risk factor of hematological diseases is reviewed and illustrated by recent cases. The hematopoietic disorders induced by benzene are manifested usually several mo to decades after exposure and are irreversible disturbances of the hemopoietic stem cells (erythropoietic, monocytopoietic, granulocytopoietic, and thrombocytopoietic cell lines), mostly with predominance of one of these myeloproliferative cell systems. Three different clinical pictures can be observed in the course of the further progression: aplastic bone marrow syndrome (aplastic anemia), hematopoietic dysplasia (preleukemia), and acute leukemia (erythroleukemia, myeloblastic, promyelocytic, or myelomonocytic forms). Transition from one clinical picture to another is also possible. Two hundred fifteen cases of disease due to benzene and its homologs were recognized in East Germany during the period 1974-1979. The analysis of 11 cases of hematological diseases due to occupational exposure to benzene showed that 4 patients were chemical workers, 5 mechanics, 1 was a painter, another an art restorer using gasoline containing benzene. The length of exposure was 0.5-45 yr. The analysis of the history of the disease in 10 cases revealed aplastic bone marrow syndrome in 6 cases (the length of exposure was 6-12 yr in 3/6); preleukemia in 6, including 3 patients who developed preleukemia after aplastic bone marrow syndrome; acute leukemia in 3 patients after exposure for 5-45 yr, and chronic myeloid leukemia in 1 patient after exposure for 9 yr. The patients with acute leukemia included one in which leukemia was preceded by preleukemia and aplastic bone marrow syndrome. (7 Refs) (In GER)

32. QUINONE-STIMULATED SUPEROXIDE FORMATION BY SUBCELLULAR FRACTIONS, ISOLATED HEPATOCYTES, AND OTHER CELLS.

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Mol Pharmacol; 20(2):387-394 1981

The influence of intracellular enzyme levels and the one-electron reduction potential of quinone (Q) substrates on cellular free radical formation was studied, using superoxide formation as a measure of total free radical. Superoxide anion radical (SAR) is formed when Qs undergo enzymatic one electron reduction to semiquinone radical, which in turn reacts with molecular oxygen, transfers an electron, and forms SAR. Isolated hepatocytes do not liberate appreciable amounts of SAR. Simple Qs stimulate such formation up to 15 nanomoles/min/10(6) cells; formation is max at Q one-electron reduction potential (ERP) of-70 millivolt (mV). Microsomal NADPH-cytochrome P-450 reductase production of SAR reaches max at a Q ERP of-200 mV. Phenobarbital induction, which increases NADPH-cytochrome P-450 reductase, has no effect on SAR formation by hepatocytes. Thus it is not rate-limiting for SAR formation. Similarly ethanol has no effect on hepatocyte SAR formation, suggesting that intracellular NADH is not rate-limiting. Effects of sulfonated stilbenes and copper deficiency were studied. Murine leukemia P-388 cells had low rates of Q-stimulated SAR formation, but C3H/10T1/2, AKR, and chemically transformed AKR murine embryonal cells exhibited rates of Q-dependent SAR formation similar to those seen with hepatocytes. Max SAR formation occurred at ERP of approx-70 mV in all cases. (30 Refs)

33. CARCINOGENICITY OF BENZIDINE, N,N'-DIACETYLBENZIDINE, AND N-HYDROXY-N,N'-DIACETYLBENZIDINE FOR FEMALE CD RATS.

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Carcinogenesis; 2(8):747-752 1981

Female CD rats were given twice-weekly ip injections for 4 wk, beginning at 30 days of age. Each of nine groups was given one of the following doses: 20 or 70 umol benzene (BZ)/mg body wt/ injection; 7, 22, or 70 umol N,N'-diacetylbenzene (DAB)/kg; or 7, 22, or 70 umol N-hydroxy-N,N'-diacetylbenzene (HDAB)/kg. A toxicity test showed HDAB to be the most toxic of the three compounds, producing chemical peritonitis and death in all animals given the higher dosage. Additional groups were given 10 or 30 umol of one of the three compounds. Toxicity was low in all groups. BZ and HDAB showed about equal carcinogenicity. The higher dose of BZ produced mammary tumors, classified as fibroadenomas or adenocarcinomas, in 41% of the animals tested. The same dose produced Zymbal's gland tumors, classified as adenomas or carcinomas, in 24% of the animals tested. DAB and HDAB appeared to be as potent as BZ in inducing tumors. HDAB produced local reactions in the peritoneum, indicating that it may be an activated carcinogenic form of BZ. (33 Refs)

DRUGS, COSMETICS, DETERGENTS AND OTHER COMMERCIAL MATERIALS

34. SISTER CHROMATID EXCHANGE INDUCED BY ANTI-HERPES DRUGS.

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Br Med J; 283(6295):817-818 1981

The rate of sister chromatid exchange induced by several anti-herpes agents was measured to assess their potential mutagenicity. The agents 5-iodo-deoxyuridine (IDU), 5-trifluoromethyl-deoxyuridine (TFT), and [E]-5-(2-bromovinyl)-deoxyuridine (BVDU)-were incubated at various concentrations with human lymphocytes and fibroblasts, and the rate of sister chromatid exchanges was measured. In lymphocytes and fibroblasts BVDU and IDU did not induce exchange except at concentrations of 50 mg/l, while TFT increased the rate of exchange at a concentration of 0.5 mg/l. The rate of sister chromatid exchange is a sensitive index of chromosomal damage, and these findings provide information on the safety of some of the anti-herpes agents tested. TFT increased the rate of exchange at a concentration that coincides with its minimal anti-viral concentration, but BVDU did not induce exchange at therapeutic concentrations. (Author abstract) (5 Refs)

35. MODULATION OF IN VITRO TRANSFORMATION AND THE EARLY AND LATE MODES OF DNA REPLICATION OF UV-IRRADIATED SYRIAN HAMSTER CELLS BY CAFFEINE.

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Radiat Res; 87(3):565-575 1981

The relationship between the effect of caffeine (CF) on post-UV DNA synthesis and its effects on transformation were studied in fresh tertiary Syrian hamster embryo cells (HEC). When HEC treated with 3 joules/square meter radiation were incubated in the presence of CF (0.25 milliM) for 48 hr, the UV-induced transformation frequency was 2-5-fold higher than that obtained with UV irradiation alone. The degree of enhancement by CF was dependent on the interval between UV irradiation and CF addition. Thirty min after HEC were UV-irradiated, the pulse-labeled DNA nascent strands were much smaller than the nonirradiated controls. The addition of CF immediately after UV irradiation had little or no effect on the size of nascent strands during the first 1.5 hr. However, the recovery of size of the nascent strands observed 5-7 hr post-UV was inhibited by CF. Thus. CF inhibited the occurrence of the late mode of replication. During the early mode of replication CF inhibited the rate of elongation of nascent daughter strands in UV-irradiated HEC. CF inhibited the enhancement of chain elongation associated with pretreatment by low UV dose, but had no effect on the size distribution of nascent strands in cells that were pulse-labeled at 0.5 hr post-UV but not chased. CF was also able to convert the late-mode replication back to the early mode. (19 Refs)

36. FACTORS AFFECTING THE DISTRIBUTION OF TOBACCO SMOKE-INDUCED LESIONS IN THE RODENT LARYNX.

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Toxicol Lett; 9(2):189-194 1981

Results of a series of tobacco smoke experiments in which Sprague-Dawley rats were exposed for either 6 or 12 wk and Syrian golden hamsters for 10 wk are reported. In the rat experiments, animals were exposed to 6% vol for vol (v/v) tobacco smoke at two dose levels: 4 x 10 min/day (high dose) and 2 x 10 min/day (low dose). Hamsters were exposed to 7% v/v tobacco smoke at two dose levels: 2 x 30 min/day (high dose) and 1 x 30 min/day (low dose). Exposure was for 7 days/wk to flue-cured tobacco cigarettes with 12 mg tar yield in rodent smoking machines. Within the larynges of rats exposed to high-dose level tobacco smoke for both 6 and 12 wk, hyperplasia with superficial keratinization of squamous epithelium was found over the cranial epiglottis, inner aspects of the arytenoid projections, lateral ventricles, and ventral aspect at the base of the epiglottis. The squamoid epithelium of the vocal folds was also hyperplastic. In rats from the low-dose level, changes were less severe and less extensive. Hamsters from the high-dose level had hyperplasia with superficial keratinization of the squamous epithelium in the cranial portion of the epiglottis and the ventral aspect of the lower epiglottis extending to the ventral pouch. Squamous metaplasia occurred in the respiratory epithelium of the ventrolateral aspect at the base of the epiglottis and also extended caudally to the ventral pouch. Low-dose group hamsters exhibited less severe laryngeal lesions. (18 Refs)

37. CARCINOMA OF THE ORAL CAVITY IN RELATION TO SMOKING, AHH-INDUCIBILITY AND ORAL HEALTH.

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Lakartidningen; 78(35):2953-2957 1981

Etiological factors, some clinical details, and methods and results of treatment of carcinoma of the oral cavity have been investigated and evaluated in a consecutive material of 20 cases seen at the departments of oto-rhinolaryngology and oral surgery, Malmo General Hospital, between the yr 1976-1979. Sixteen of the patients were male, 4 female. The av age was 64.7 yr. All men and two of the women were smokers. In the male patients, there was an overrepresentation of heavy alcohol consumers. The tumor localization involved the tongue in 11 of the cases. Thirteen of the tumors were advanced but resectable, while 2 were non-resectable. The aryl-hydrocarbonhydroxylase (AHH) inducibility was investigated in the material and there was a statistically significant (p less than 0.001) overrepresentation of cases with high AHH-inducibility and an underrepresentation of cases with low AHH-inducibility. It is concluded that smoking is an important exogenous factor associated with the development and course of oral cancer, and that high AHH inducibility may be a genetically determined, constitutional background to increased susceptibility for smoke-dependent carcinogenesis in the oral cavity. (Author abstract) (15 Refs) (In SWE)

38. CONTRASTING EFFECTS OF MAYTANSINE AND VINBLASTINE ON THE ALKYLATION OF TUBULIN SULFHYDRYLS.

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Dept. Biochemistry, Univ. Texas Health Science Center, San Antonio, TX, 78284

Arch Biochem Biophys; 210(2):498-504 1981

The effects of maytansine (MAY) and vinblastine (VIN) on the accessibility of the sulfhydryl groups were compared. MAY and VIN both bind to tubulin, are competitive inhibitors of each other's binding, and strongly inhibit microtubule assembly in vitro, but MAY (unlike VIN) does not induce tubulin aggregation or stabilize colchicine binding. VIN (10 uM) inhibited the reaction of bovine brain tubulin with 14C-iodoacetamide by 45%; MAY (up to 100 uM) had no effect; but MAY was a potent inhibitor of VIN's effect. This competition is consistent with a model in which the two drugs compete for the same or overlapping sites but suggests that the nature of the binding of each drug is different. The suppression of alkylation of tubulin induced by colchicine or podophyllotoxin was not affected by MAY, suggesting that MAY and VIN bind to different sites. Both MAY and VIN were able to increase the formation of beta-ef (an electrophoretically faster migrating form of beta-tubulin that apparently contains an intrachain crosslink) by the bifunctional reagent N,N'-ethylenebis-(iodoacetamide), showing that, at least in the portion of the tubulin molecule involved in beta-ef formation, VIN and MAY have similar effects. Since MAY does not seem to suppress competing alkylation reactions, the enhancement of beta-ef formation may represent a genuine conformational effect. Since the sulfhydryl groups of tubulin may be involved in regulating microtubule assembly, MAY and VIN may differ in the manner in which they inhibit microtubule assembly. (18 Refs)

39. HEMATOPOIETIC DISORDERS RESULTING FROM CYTOSTATIC TREATMENT.

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Cas Lek Cesk; 120(25):769-773 1981

Hematopoietic disorders due to cytostatic treatment are reviewed. Impaired hematopoiesis is one of most frequent side-effects of antitumor chemotherapy as an inherent result of nonselective inhibition of proliferating cells. Such drugs as bleomycin, dacarbazine, L-asparaginase, and cis-platinum have only a slight effect on both proliferating and resting hemopoietic cells, while folic acid antagonists (methotrexate), mercaptopurine, cytosine arabinoside, vinca alkaloids (vinblastine and vincristine), and hydroxyurea have a much stronger effect on proliferating than on resting hemopoietic cells. Busulfan, nitrogen mustard, and trichloromethine have noticeable effects on both cell lines, but affect resting cells more strongly than proliferating ones, while cyclophosphamide and adriamycin affect proliferating cells more strongly than resting ones. Nitrosoureas (carmustine and lomustine) affect proliferating and resting cell equally strongly. Transfusion of blood or leukocyte concentrate, corticoid or lithium carbonate treatment are available for the treatment of granulocytopenia induced by cytostatics. Substitution treatment or drug stimulation is indicated for the treatment of thrombocytopenia. Androgens (testosterone) are effective in the treatment of anemia. (18 Refs) (In CZE)

40. MODIFICATION OF THE MUTAGENICITY AND TERATOGENICITY OF CYCLOPHOSPHAMIDE IN RATS WITH INDUCERS OF THE CYTOCHROMES P-450.

Hales BF

Dept. Pharmacology and Therapeutics, McGill Univ., Montreal, Quebec H3G 1Y6, Canada

Teratology; 24(1):1-11 1981

The chemotherapeutic agent cyclophosphamide (CP) may act as a carcinogen if it is enzymatically metabolized to reactive intermediates with alkylating, mutagenic, or cytotoxic effects, which activation is thought to be catalyzed by the cytochrome P-450 monooxygenase system. Phenobarbital (PB) induces the hepatic cytochrome P-450 that is involved in the activation of CP to both alkylating and mutagenic metabolites; beta-naphthoflavone (bNF) induces a different cytochrome P-450 and actually decreases the activation of CP by liver microsomes. Using rats pretreated with either PB or bNF, the activation of CP to mutagenic metabolites by enzyme fractions on day 13 of gestation was measured with the Ames test on Salmonella typhimurium TA1535 and teratogenicity was assessed in vivo by treatment of rats with CP on day 13 of gestation. CP was activated to mutagenic metabolites to the same extent (on a tissue wet wt basis) by enzyme fractions from maternal liver, kidney, and placenta, despite differences in cytochrome P-450 content, but fetal homogenates did not activate CP. PB pretreatment increased the liver cytochrome P-450 content 1.8-fold and the activation of CP by maternal liver microsomes 10-fold; however, PB did not alter the activation of CP by maternal kidney, by placenta, or by the fetus. PB pretreatment increased the teratogenicity of CP as measured by an increased incidence of malformed embryos or by decreased fetal wt. Pretreatment with bNF did not induce the hepatic cytochrome P-450 in the pregnant rat; did not change the activation of CP to mutagenic metabolites by liver, kidney, the placenta, or the fetus; and had no effect or decreased the teratogenicity of CP. These results suggest that the mother, rather than the fetus, is the site of PB activation; that the principal site of activation is the maternal liver; and that there is a correlation between the teratogenicity and mutagenicity of CP after induction by cytochrome P-450. (36 Refs)

41. THE EFFECT OF PHENFORMIN, L-DOPA AND PARACHLOROPHENYLALANINE TREATMENT OF IMMUNE RESPONSE AND CHEMICAL CARCINOGENESIS DEVELOPMENT IN BALB/C MICE.

Vinnitsky VB, Yakimenko VA

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Vopr Onkol; 27(6):45-50 1981

Treatment with 20-methylcholanthrene resulted in the increase in hypothalamic levels of noradrenaline and serotonin in BALB/c mice. Immunization of carcinogen-treated animals with ovine RBCs was followed by changes in the hypothalamic levels of central neurotransmitters, opposite to those in intact immunized controls. After correction of the levels of neurotransmitters in the hypothalamus with phenformin, parachlorophenylalanine or L-dopa carried out prior to immunization, the fraction of antibody-producing cells in the spleen of carcinogen-treated mice returned to normal. A combined administration of immunostimulators and drugs for correction of hypothalamic levels of noradrenaline and serotonin potentiated inhibitory effect of the former on chemical carcinogenesis. (Author abstract) (15 Refs) (In RUS)

42. CYST FORMATION IN RAT KIDNEY INDUCED BY CIS-PLATINUM ADMINISTRATION.

Dobyan DC, Hill D, Lewis T, Bulger RE

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Lab Invest; 45(3):260-267 1981

The long-term pathologic effects of the antitumor drug cis-diamminedichloroplatinum II (CP) on the structure of the rat kidney were investigated. Light microscopy and transmission and scanning electron microscopy were used to characterize the morphologic changes 2 wk, 4 wk, and 6 mo after ip injection of CP to rats. At all time intervals examined, the S3 segment of the proximal tubule located in the outer stripe of the medulla showed the most consistent pattern of injury. Two wk after CP, the proximal tubules located in the outer stripe region as well as the medullary rays were widely dilated and lined by low-lying epithelial cells, many of which contained large atypical nuclei. Many tubules still showed evidence of necrosis, whereas other tubules appeared to be undergoing atrophic changes. After 4 wk, proximal tubular dilation continued resulting in the formation of numerous microcysts in the region of the outer stripe. These changes appeared to progress, and after 6 mo large cysts (mean diameter 2,152 +-1,241 um) were identified which involved the entire outer stripe, with many of these cysts extending to the subcapsular cortex. The kidneys at this time period showed a pattern of chronic renal injury in the outer stripe, and this damage was now also observed in the cortex. In several animals, small foci of abnormal foam cells surrounded by a basal lamina could be identified. We conclude that CP has a pronounced long-term effect and causes cyst formation in the rat kidney. (Author abstract) (22 Refs)

43. DNA SUPERCOILING, SHORTENING, AND INDUCTION OF SINGLE-STRAND REGIONS BY CIS-DIAMMINEDICHLOROPLATINUM(II).

Mong S, Daskal Y, Prestayko AW, Crooke ST

Bristol-Baylor Lab., Dept. Pharmacology, Baylor Coll. Medicine, Houston, TX, 77030

Cancer Res; 41(10):4020-4026 1981

The compound cis-diamminedichloroplatinum(II) (CDDP) was found to bind to covalently closed circular supercoiled, covalently closed circular nonsupercoiled, and single-strand broken relaxed PM2 DNA and induce different types of DNA conformational changes. Using Kleinschmidt's technique, it was found that binding of CDDP decreased the DNA length to 75% of the original single-strand broken relaxed DNA without inducing superhelical conformational changes. CDDP also shortened the length of covalently closed circular nonsupercoiled DNA before a supercoiled conformation was generated. Single strand-specific nucleases were used to detect drug-induced DNA structural alterations. Local single-strand regions or regions of denaturation were detected by S1 nuclease from Aspergillus oryzae and by BAL-31 nuclease from Alteromonas espejiana BAL-31. The single-strand regions or local denaturation regions do not seem to be related to or caused by DNA superhelical conformational changes since they were detected at drug concentrations at which no significant DNA superhelical turns were found. DNA shortening, superhelical conformational changes, and local denaturation regions can be explained by the previously proposed 'DNA intrastrand cross-linking' model. (Author abstract) (31 Refs)

44. ETHANOL-INDUCED CELL SENSITIZATION TO BLEOMYCIN CYTOTOXICITY AND THE INHIBITION OF RECOVERY FROM POTENTIALLY LETHAL DAMAGE.

Mizuno S

Dept. Antibiotics, Natl. Inst. Health, Shinagawa-ku, Tokyo 141, Japan

Cancer Res; 41(10):4111-4114 1981

The cytotoxic effect of bleomycin toward mouse mammary carcinoma FM3A cells in culture was markedly potentiated by exposure of the cells to ethanol either before or after treatment with bleomycin. Ethanol-induced cell sensitization to bleomycin cytotoxicity produced a decrease in cell survival which became dependent on dose and time of drug treatment. The sensitizing effect of ethanol after drug treatment was max when ethanol exposure immediately followed drug treatment, and it rapidly decreased as the time interval between the two treatments was increased. Ethanol did not sensitize cells to the cytotoxic effects of cis-diamminedichloroplatinum(II) and macromomycin. These results are discussed in terms of the ability of ethanol to inhibit cell recovery from potentially lethal damage after bleomycin treatment. (Author abstract) (29 Refs)

45. LEVAMISOLE AND SODIUM DIETHYLDITHIOCARBAMATE.

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Trends Pharmacol Sci; 2(9):248-249 1981

Problems in the relatively new field of immunopharmacology are illustrated by a review of experiences with the immunological enhancing agents levamisole (LV) and sodium diethyldithiocarbamate (DTC). Ideally, such agents should lack carcinogenicity or tumor enhancing effects, be devoid of antigenicity and sensitizing effects, exhibit known effects on various populations and subsets of immunocompetent cells, and be of known toxicity and pharmacological effects. Despite lack of information about the LV mode of action, need for active cancer therapy triggered a variety of clinical trials; many did not refer to available laboratory data or attempt to determine suitable dose, and only occasional studies accounted for immunological status of the patient. DTC has resulted from the translation of experimental data into clinical experience, making available a synthetic, chemically-defined compound devoid of undesirable cholinergic-like effects. Rodent studies indicate lack of carcinogenicity after daily feeding of DTC for 104-109 wk. DTC exerts a protective effect against some chemically-induced tumors and against ionizing radiation. At immunostimulant doses (0.5-25 mg/kg) the purified drug is essentially without toxicity or side effects . Modification of a patient's immune system is the ultimate hope of immunotherapy for treatment and even cure of cancer. (10 Refs)

46. CARCINOGENICITY OF HYDANTOINS: DATA, HYPOTHESES, AND PUBLIC REVIEWS.

Scoville B, White BG

Natl. Inst. Neurological and Communicative Disorders and Stroke, NIH, Bethesda, MD, 20205

Psychopharmacol Bull; 17(3):195-197 1981

The Epilepsy Branch of NIH undertook an independent literature review of 353 studies of phenytoin (PT) because the International Agency for Research on Cancer had initially classified it as a carcinogen in 1977 but reversed its position in 1978. Five types of lymph node changes have been reported to be associated with PT use: acute benign enlargements, subacute reactions (to which the term pseudolymphoma has been applied), lymphoma (79 cases; the causal relationship to PT was not clear), pseudopseudolymphoma, and immunoblastic or angioimmunoblastic lymphadenopathy. There have been four case reports of neuroblastoma in very young children born to mothers who had taken PT during pregnancy (3 fetal hydantoin syndrome and 1 cleft palate). Among 11 epidemiological studies, 4 case-control studies were positive while 7 cohort studies were negative. The risk of lymphoma from antiepileptic drugs may be 10 x that in the general population but not higher than 1/1,000. Two positive animal toxicity studies exist: one showed a decreased latency of reticulum cell sarcomas in SJF/J mice treated with PT for greater than 1 yr, and the other revealed a 25% incidence of lymphosarcoma, reticulosarcoma, or leukemia, in PT-treated mice compared with 5% in controls. PT impairs the immune system and may act as an antigenic stimulus; both of these effects may contribute to its possible carcinogenicity. Experts at NIH and at the Food and Drug Administration find that the data on PT are inconclusive. (15 Refs)

47. SODIUM PENTACHLOROPHENATE AS A MUTAGENIC AGENT.

Roy P, Kundu P, Das A

Dept. Microbiology, Bose Inst., 93/1, A. P. C. Road, Calcutta-700009, India

Biotechnol Lett; 3(8):401-404 1981

The frequency of auxotrophic mutants of Aspergillus niger strain 350 due to UV irradiation (254 nanometer; 4-16 min; 10(-5) joules/square mm/sec) followed by sodium pentachlorophenate (SPCP) treatment (48 hr at 0.5% in liquid medium), due to UV treatment alone (same conditions), and due to SPCP treatment alone (0.5% for 1 hr in liquid medium) were compared with controls. Although SPCP treatment enhanced the frequency of auxotrophic mutants created by UV irradiation, SPCP alone also acted as a mutagen, producing both auxotrophs and other types of mutants. (7 Refs)

48. ULTRASTRUCTURE OF HEPATIC ANGIOSARCOMA IN RATS INDUCED BY VINYL CHLORIDE.

Spit BJ, Feron VJ, Hendriksen CF

Institute CIVO-Toxicology and Nutrition TNO, P.O. Box 360, 3700 AJ Zeist, The Ne therlands

Exp Mol Pathol; 35(2):277-284 1981

The hepatic angiosarcoma studied was from a male Wistar rat having been exposed to vinyl chloride monomer (VCM) by the oral route for 120 wk. Widened sinusoids lined by large electron-lucent, spindle-shaped tumor cells and membrane-bound nuclear-free structures were seen in the transitional zone between the tumor mass and the adjacent liver tissue. In areas merely consisting of tumor tissue the tumor cells had a more angular or irregular shape. The origin of the tumor cells is discussed in light of the characteristic differences between endothelial cells and Kupffer cells described in the literature. Although an endothelial origin of the tumor cells could not be established unequivocally, it was concluded that at present there is little reason to doubt such an origin. (Author abstract) (21 Refs)

49. DIFFERENTIATION OF THE MECHANISMS OF ONCOGENICITY OF 1,4-DIOXANE AND 1,3-HEXACHLOROBUTADIENE IN THE RAT.

Stott WT, Quast JF, Watanabe PG
Toxicology Res. Lab., Dow Chemical U.S.A., Midland, MI, 48640
Toxicol Appl Pharmacol; 60(2):287-300 1981

Two tumorigenic agents, 1,4-dioxane (DX) and 1,3-hexachlorobutadiene (HCBD) were compared to the known mutagen dimethylnitrosamine (DMN) to determine whether their actions were by a genetic or nongenetic mechanism. Male Sprague Dawley rats were given tumorigenic doses of DX in drinking water (0, 10 or 100 mg/kg/day for 11 wk), HCBD by gavage (0, 0.2, or 20 mg/kg/day for 3 wk), or DMN by gavage (3 mg/kg/day for 3 wk). Other groups of rats were given single doses of DX (10, 100, 1,000 mg/kg), HCBD (0.2, 20 mg/kg), or DMN (3 mg/kg) by gavage. DX produced no genotoxic effects at tumorigenic doses. A single large dose produced no alkylation of DNA or increase in DNA repair. Repeated high doses of DX were hepatotoxic. HCBD produced a minor genotoxic effect compared with DMN. DNA repair in renal tissue was increased 1.27-1.54-fold by HCBD (20 mg/kg); DNA alkylations occurred at the rate of 0.78 per 10(6) nucleotides. No mutations were produced in the Ames' bacterial mutagenesis assay. HCBD produced renal cytotoxicity. Apparently DX induces tumors by a nongenetic mechanism. HCBD acts primarily in a nongenetic way, but is weakly genotoxic. Risk from either compound is likely only at cytotoxic doses. (34 Refs)

50. ANTIMUTAGENIC ACTIVITY OF CERTAIN DRUGS.

Ostrovskaia AA, Lil'in ET, Glazyrin VF
Lab. Genetical Control of Drug Metabolism, Res. Inst. Biological Tesing of Chemical Compounds, Kupavna, Moscow Oblast', USSR
Farmakol Toksikol; 44(4):467-470 1981

The antimutagenic activity of 11 drugs was studied in cultures of human embryonal fibroblasts (HEF) and xeroderma pigmentosum (XP) cells. Caffeine, hexamidine, LM8 and vitamin E stimulated proliferation of both HEF and XP cells. Ionol stimulated proliferation of HEF but was ineffective in a culture of XP cells. Mutagen dioxidine caused marked inhibition of proliferation of HEF but did not affect proliferation of XP cells. (5 Refs) (In RUS)

51. MUTAGENICITY OF CHEMICALS OF INDUSTRIAL AND AGRICULTURAL RELEVANCE IN SALMONELLA, STREPTOMYCES AND ASPERGILLUS.

Principe P, Dogliotti E, Bignami M, Crebelli R, Falcone E, Fabrizi M, Conti G, Comba P
Istituto Superiore di Sanita, Viale Regina Elena 299-00161, Rome, Italy
J Sci Food Agric; 32(8):826-832 1981

Ethylene dibromide (EDB), ethylene dichloride (EDC), propylene dichloride (PDC), allyl alcohol (AA), and sulfallate (S) were tested for their ability to induce reverse mutations (his+ revertants) in Salmonella typhimurium, forward mutations (streptomycin resistance) in Streptomyces coelicolor, and point mutations (8-azaguanine resistance) in Aspergillus nidulans. EDB and S strongly reverted S typhimurium strains TA100 and TA1535;, PDC had a weak effect on these strains; and EDC was weakly active in TA1535 following microsomal activation with rat liver S-9 mix. This mix reduced the mutagenicity of EBD but not that of S. In S coelicolor, EDB was positive only in spot test experiments and S was weakly positive in plate tests; EDC and PDC were inactive in both test systems.

In A nidulans, EDB and PCB gave positive responses in the plate and spot tests and S gave a positive response only in the spot test. AA was was not mutagenic in any of the genetic systems. (21 Refs)

REVIEWS AND OTHER COMPOUNDS

52. EXPERIMENTAL DATA ON MUTAGENIC ACTIVITY OF TOLUENE, ISOPROPANOL AND SULFUR DIOXIDE.

Aristov VN, Red'kin IuV, Bruskin ZZ, Ogleznev GA
Medical Inst., Omsk, USSR
Gig Tr Prof Zabol; (7):33-36 1981

The mutagenic activity of toluene (TL), isopropanol (IP) and sulfur dioxide was studied in albino rats subjected to a 4-mo inhalation exposure to test substances. Cytogenetic analysis of bone marrow cells showed significantly increased level of aberrant metaphases after exposure to TL and IP. Ineffective concentrations of TL and IP were 2.6 and 0.52 mg/ cubic meter, respectively. (8 Refs) (In RUS)

53. TRANSFORMATION OF HAMSTER EMBRYO CELLS BY NEUTRAL STEROLS AND BILE ACIDS.

Kelsey MI, Pienta RJ
NCI, Landow Building, Room 8C25, Bethesda, MD, 20205
Toxicol Lett; 9(2):177-182 1981

Toxicity and transformation data on the neutral sterols cholesterol-alpha-epoxide and cholestan-3beta,5alpha, 6beta-triol (Triol), and on primary (cholic and chenodeoxycholic) and secondary (lithocholic and deoxycholic) bile acids are presented. Previous results showed that 10 ug/ml cholesterol is neither toxic nor cell- transforming. Cholesterol-alpha-epoxide was toxic to 50% (TD50) of cultured Syrian hamster embryo cells at 10 ug/ml, whereas TD50 for Triol occurred at a concentration 1/5 that of its precursor. In the bile acid series, the primary bile acids were less toxic than the secondary derivatives. The latter were less toxic than the oxygenated sterols. Transformation occurred at all doses tested for the oxygenated sterols. Relative cloning efficiencies compared with those found for controls at the highest doses tested were 87% and 70% for cholesterol-alpha-epoxide and Triol, respectively. The primary bile acids were toxic at 480 ug/ml (cholic acid) and 208 ug/ml (chenodeoxycholic acid), and deoxycholic acid had a cloning efficiency of 82% at the highest dose causing cell transformation. Results indicated that mammalian cell transformation may be a preferable short-term assay for structure-activity information of steroid derivatives as well as for potential carcinogenicity. (23 Refs)

54. A CASE-CONTROL STUDY OF BLADDER CANCER IN THE UNITED STATES RUBBER AND TYRE INDUSTRY.

Checkowway H, Smith AH, McMichael AJ, Jones FS, Monson RR, Tyroler HA
Occupational Health Studies Group, Sch. Public Health, Univ. North Carolina, Chapel Hill, NC, 27514
Br J Ind Med; 38(3):240-246 1981

A case-control study of bladder cancer was conducted in five United States rubber and tire companies to determine if there were high-risk jobs and work areas within the industry. The study included 220 male cases of bladder cancer, of whom 107 were identified from hospital record reviews and 113 from death certificates. Each case was matched individually with two industry controls by sex, race, yr of birth, and company. One control was matched additionally by yr of hire and duration of employment. Comparisons of cases and controls not matched by yr of hire and age of hire showed no differences for those variables, which suggests that age and calendar period of first exposure to the industry were not risk determinants. When the work histories of both cases and controls were contrasted it was found that cases were more likely than controls to have worked in milling (odds ratio (OR) = 1.91) and calender operation (OR = 2.21) jobs. The relative risk estimates for milling and calender operation both exhibited linear trends of increase with duration of exposure. Milling and calender operation jobs entail potential exposures to volatilized reaction products from heated rubber stock. A better understanding of etiological associations with job type will require more detailed characterization of the work environment with regard to the sources and levels of aromatic amines and other suspected bladder carcinogens. (Author abstract) (25 Refs)

55. EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.

International Agency for Research on Cancer
International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum; 26:1-411 1981

Eighteen monographs present experimental and human data for the following antineoplastic and immunosuppressive agents: 5-azacytidine, azathioprine, bischloroethyl nitrosourea, bleomycins (sulfates and hydrochlorides), chlorambucil, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, cisplatin, cyclophosphamide, dacarbazine, 5-fluorouracil, isophosphamide, 6-mercaptopurine, methotrexate, prednisone, procarbazine hydrochloride, treosulfan, vinblastine sulfate, and vincristine sulfate. Section 1 of each monograph summarizes chemical and physical properties; Section 2 describes production, use, occurrence, and analysis. Section 3 covers biological data relevant to evaluation of carcinogenic risk in humans, including carcinogenicity studies, toxic effects, metabolic data, mutagenicity and other short-term tests, and when available case reports or epidemiological studies of cancers present in patients treated with the compound. Section 4 summarizes pertinent animal and human data and gives critical views of the IARC Working Group. (1452 Refs)

56. STRUCTURE ACTIVITY RELATIONSHIPS IN EXPERIMENTAL NEURO-ONCOLOGY.

Schreiber D, Mendel J, Heiderstadt R
Institut fur Allgemeine Pathologie und Pathologische Anatomie, Medizinische Akademie Erfurt, Nordhauser Strasse 74, DDR-5060 Erfurt, E. Germany
Arch Geschwulstforsch; 51(7):597-603 1981

The neurocarcinogenic effects of the neurotropic ultimate carcinogens ethylmethane sulfonate (EMS) and methylmethane sulfonate (MMS) were studied in inbred hooded rats. In postnatal experiments, MMS was administered iv in doses of 0.45 millimole (mmole) at 14-day intervals (total dose 6.82 mmoles), and EMS in doses of 0.89 mmole at 14-day intervals (total dose 13.31 mmoles). In the prenatal (transplacental) experiments, MMS and EMS were administered in the respective single doses of 0.27 mmole and 0.81 mmole on day 21 of pregnancy. The numbers of tumor-bearing animals were 18/28 (64.3%) and 12/38 (31.6%) after postnatal and prenatal treatment with MMS, respectively, and 24/28 (85.7%) and 5/32 (15.6%) after postnatal and prenatal treatment with EMS. The number of animals with neurogenic tumors was 17/28 (60.7%) and 7/38

(18.4%) after postnatal and prenatal treatment with MMS, and 23/28 (82.1%) and 3/32 (9.4%) after postnatal and prenatal treatment with EMS. The tumors included astrocytomas, oligodendrogliomas, sarcomas, and unclassified tumors of the brain and spinal cord, and intracranial as well as peripheral neurinomas. The findings contradict data in the literature, according to which ultimate carcinogens containing ethyl groups have a stronger prenatal neurocarcinogenic effect than compounds with methyl groups, while the latter are more neurocarcinogenic than compounds with ethyl groups in adult animals. Further investigations will be necessary to determine, if EMS and MMS represent exceptions, or whether there are other pa irs of ethyl and methyl compounds with similar patterns of neurotropic effect. (29 Refs) (In GER)

57. ALTERATIONS IN DRUG-METABOLIZING ENZYMES DURING FEEDING OF THE CARCINOGEN 2-AMINOANTHRAQUINONE.

Ramanathan R, Reddy TV, Weisburger EK
Lab. Carcinogen Metabolism, NCI, Bethesda, MD, 20205
Toxicol Appl Pharmacol; 60(2):204-212 1981

Changes in enzymes which metabolize drugs during periods of feeding with 2-aminoanthraquinone (AAQ), at carcinogenic levels, were studied in young female Fischer 344 rats. Rats were fed 2% AAQ for 2, 4, 8 or 14 wk; after treatment, some were returned to the control diet. Some rats on the control diet were pair-fed with the AAQ group. At least four rats were available for each enzyme determination. Controls were fed ad libitum. Feeding AAQ increased liver content of cytochrome P-450, cytochrome b5, and increased NADPH-cytochrome c reductase activity as early as 2 wk. After 4 wk of AAQ, there was no change in azodye reductase, although an increase was observed in pair-fed controls. However, after 8 and 14 wk of AAQ, there was a significant increase in dimethylaminoazobenzene reductase. AAQ feeding also led to increased activities of benzo(a)pyrene hydroxylase, epoxide hydrolase, and alpha-naphthol-O-glucuronyl transferase. AAQ feeding beyond 4 wk increased the activities of N-demethylases, aniline hydroxylase and azo reductase. After the experimental period of AAQ feeding, the measured enzyme activities during the recovery period remained elevated in rats fed AAQ for 14 wk for 1 or 2 wk, and 2-4 wk in rats fed AAQ for 8 wk. (22 Refs)

58. CARCINOGENIC EFFECT OF 1,3 PROPANE SULTONE.

Gupta SC, Mehrotra TN, Srivastava UK
M. L. N. Medical Coll., Allahabad, India
Int Surg; 66(2):161-163 1981

Eighty animals were administered propane sultone in either single or multiple doses. The skin lesions at the site of injection were due to necrosis, ulceration, destruction of the underlying muscle and varying grades of fibrosis. In 13 rats, pseudosarcomatous changes were seen, the duration of which varied from 21 to 25 wk after the first injection. Systemic examination revealed neoplastic pulmonary lesions in 17 rats that had been injected with propane sultone 21 to 25 wk previously. The malignancies varied from adenocarcinoma to anaplastic carcinoma. Malignancy of lungs is here reported for the first time. (Author abstract) (3 Refs)

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CHEMICAL CARCINOGENESIS

1. TOXICOLOGICAL ASPECTS OF POLYCYCLIC AROMATIC HYDROCARBONS (PAH).

De Fernicola NA, De Azevedo FA
Divisao de Toxicologia e Ecotoxicologia, Diretoria de Tecnologia e Desenvolvimento, Sao Paulo, Brazil
Rev Bras Saude Ocup; 33(9):62-68 1981
In POR

2. EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.

International Agency for Research on Cancer
International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum; 26:1-411 1981

3. STUDIES ON THE ROLE OF ORAL CONTRACEPTIVE USE IN THE ETIOLOGY OF BENIGN AND MALIGNANT LIVER TUMORS.

Mettlin C, Natarajan N
Cancer Control and Epidemiology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Surg Oncol; 18(1):73-85 1981

RADIATION CARCINOGENESIS

4. EXPERIMENTAL RADIATION CARCINOGENESIS: WHAT HAVE WE LEARNED?

Fry RJ
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Radiat Res; 87(2):224-239 1981

5. INFLUENCE OF NONCARCINOGENIC SECONDARY FACTORS ON RADIATION CARCINOGENESIS.

Little JB
Lab. Radiobiology, Harvard Univ., Sch. Public Health, Boston, MA, 02115
Radiat Res; 87(2):240-250 1981

6. MEDICAL IRRADIATION IN JAPAN - STOCHASTIC RISK ESTIMATION AND ITS REDUCTION.

Hashizume T
Div. Physics, National Inst. Radiological Sciences, 9-1 Anagawa 4-Chome, Chiba Shi 260, Japan
Nippon Igaku Hoshasen Gakkai Zasshi; 41(5):445-474 1981
In JPN

7. RADIOACTIVITY IN DRINKING WATER.

Cothern CR
Office of Drinking Water, Environmental Protection Agency, Washington, DC
Radioactivity in Drinking Water. Available from National Technical Information Service, Springfield, VA, as PB81-192833:, 79 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

8. EPIDEMIOLOGY OF GASTROINTESTINAL CANCER.

Miller AB
NCIC Epidemiology Unit, Univ. Toronto, McMurrich Building, Toronto, Ontario M5S 1A8, Canada
Compr Ther; 7(8):53-58 1981

9 EPIDEMIOLOGICAL ASPECTS OF ESOPHAGEAL CANCER.

Ruggieri M, Tosato F, De Rocco K, Lepore M, Cipriano E, Paolini A
IV Cattedra di Clinica Chirurgica Generale e Terapia Chirurgica, Universita degli Studi di Roma, Rome, Italy
Recenti Prog Med; 70(5):545-556 1981
In ITA

10. PANCREATIC CANCER.

Cohn I, Hastings PR
Dept. Surgery, Louisiana State Univ., 1542 Tulane Ave., New Orleans, LA, 70112
UICC Tech Rep Ser Vol. 57, Issue 12, 142 pp., 1981.

11. GENETICALLY DETERMINED SUSCEPTIBILITY TO CANCER.

Marks PA
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Blood; 58(3):415-419 1981

12. ETIOLOGY, ROLE AND DETECTION OF CHROMOSOMAL ABERRATIONS IN MAN.

Fabricant JD, Legator MS
Dept. Preventive Medicine, Div. Environmental Toxicology, Univ. Texas Medical Branch, Galveston, TX, 77550
JOM; 23(9):617-625 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

13. INDUSTRIAL CARCINOGENESIS.

Vickers CF
Dept. Dermatology, Univ. Liverpool, Liverpool L69 3BX, England
Br J Dermatol; 105(Suppl21):57-61 1981

14. ENVIRONMENT AND HEALTH (LITERATURE REVIEW).

Khachatrian TS
Dept. Public Health, State Inst. Advanced Training for Physicians, Erevan, USSR
Zh Eksp Klin Med; 21(3):287-292 1981
In RUS

15. LIFESTYLE AND CANCER.

Higginson J
International Agency for Res. on Cancer, Lyon, France
Cancer Forum; 5(1):4-14 1981

16. ASBESTOS, AN ENVIRONMENTAL POLLUTANT.

Zamfir G, Diaconu R
Institutul de igiena si sanatate publica, Iasi, Romania
Igiena; 30(1):1-9 1981
In RUM

17. REVIEW OF UICC PROGRAM ON SMOKING AND LUNG CANCER.

Gray N
Smoking and Cancer Program, UICC, 3 rue du Conseil General, 1205 Geneva, Switzerland
Cancer Forum; 5(1):15-18 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

18. EXPERIMENTAL APPROACHES TOWARDS THE BIOCHEMICAL ANALYSIS OF CHEMICAL CARCINOGENESIS.

Laishes BA
McArdle Lab. for Cancer Res., Univ. Wisconsin Medical Sch., Madison, WI, 53706
ACS Symp Ser; 160:197-215 1981

19. FIBRONECTIN AND RELATED TRANSFORMATION-SENSITIVE CELL SURFACE PROTEINS (ONCOLOGY OVERVIEW).

International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Fibronectin and Related Transformation-Sensitive Cell Surface Proteins (Oncology Overview)/Chen, L B, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923001:; OB-81/01:95pp. 1981

20. PRENEOPLASTIC LESIONS OF THE MAMMARY GLAND. (ONCOLOGY OVERVIEW)

International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Preneoplastic Lesions of the Mammary Gland (Oncology Overview) Medina, D, ed This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-923002; OB-81/02:134pp. 1981

21. LYMPHOCYTE DIFFERENTIATION: AN ESSENTIAL BASIS FOR THE COMPREHENSION OF LYMPHOID NEOPLASIA.

Magrath IT
Pediatric Oncology Branch, Div. Cancer Treatment, NCI, NIH, Public Health Service, United States Dept. Health and Human Services, Bethesda, MD, 20205
JNCI; 67(3):501-514 1981

MODIFICATION OF CARCINOGENESIS

22. FACTORS STIMULATING AND INHIBITING TUMOR GROWTH IN CARCINOGENESIS.

Kochergina NI, Kosova IP
Res. Lab. Experimental Immunobiology, Moscow, USSR
Usp Sovrem Biol; 91(3):409-418 1981
In RUS

23. TWO INDEPENDENT ASPECTS OF TUMOR PROMOTION.

Berenblum I, Armuth V
Weizmann Inst. Science, Rehovot, Israel
Biochim Biophys Acta; 651(1):51-63 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

24. BURKITT'S LYMPHOMA.

Ziegler JL
NCI, Bethesda, MD, 20205
N Engl J Med; 305(13):735-745 1981

25. REVIEW ARTICLE. REGULATION OF EXPRESSION OF THE INTEGRATED RETROVIRUS GENOME.

Weinberg RA, Steffen DL
Center for Cancer Res., Massachusetts Inst. Technology, Cambridge, MA, 02139
J Gen Virol; 54(part1):1-8 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

26. THE DEVELOPMENT AND VALIDATION OF MUTAGENICITY SCREENING TESTS.

Durkin PR, Santodonato J
Center for Chemical Hazard Assessment, Syracuse Res. Corporation, Merill Lane, Syracuse, NY, 13210
Tappi; 64(9):153-159 1981

27. SHORT-TERM TEST SYSTEMS FOR POTENTIAL MUTAGENS AND CARCINOGENS: I. MICROBIAL TESTS (ONCOLOGY OVERVIEW).

International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Short-Term Test Systems for Potential Mutagens and Carcinogens: I Microbial Tests (Oncology Overview) Simmon, V F; Peirce, V; eds This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-922903:, OK-81/03:124pp. 1981

28. ANIMAL MODELS OF INTRA-ORAL CHEMICAL CARCINOGENESIS: A REVIEW.

Eveson JW
Dept. Oral Medicine and Pathology, Guy's Hosp., London SE1 9RT, England
J Oral Pathol; 10(3):129-146 1981

29. THE CHROMOSOMES IN HEMATOLOGY.

Berger R
Laboratoire de Cytogenetique, Institut de Recherches sur les Leucemies et les Maladies du Sang, UER d'Hematologie, Hopital Saint-Louis, 2 place du Dr. Fournier, 75475 Paris Cedex 10, France
Cancer Genet Cytogenet; 4(1):69-88 1981

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CHEMICAL CARCINOGENESIS

Miscellaneous Agents

SERIES CK13 No. 82/03

MARCH, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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HYDRAZINES AND RELATED COMPOUNDS

1. ADENOSINE AND GUANOSINE 3',5' CYCLIC MONOPHOSPHATE PHOSPHODIESTERASE ACTIVITIES IN RAT SMALL AND LARGE BOWEL FOLLOWING SINGLE AND MULTIPLE EXPOSURES TO 1,2-DIMETHYLHYDRAZINE.

Stevens RH, Loven DP, Singh D
Dept. Radiology, Radiation Res. Lab., Univ. Iowa, Iowa City, IA, 52242
Drug Chem Toxicol; 4(2):161-172 1981

The affect of the colon carcinogen, dimethylhydrazine (DMH: 20 mg/kg, sc) on the hydrolytic activities of cyclic AMP (cAMP) and guanosine 3',5'-cyclic monophosphate (cGMP) phosphodiesterases (PDE) in the small and large intestines of adult male outbred rats was determined. Following injection of DMH, an almost immediate increase in cAMP-PDE activities in the colon tissue was observed. These elevated activites, which had increased after 1 day to greater than three times that in untreated colon, returned to normal value after approx 5 days after exposure. In contrast, the cGMP-PDE activities seemed only slightly changed by the exposure to DMH. Chronic exposures at weekly intervals to the DMH had little effect on PDE activites during the early phases of tumor activity. However, at the end of wk 20, exposed colon tissues had elevated cAMP-PDE levels similar to those in cancer cells. Approx 10-15% of DMH-treated rats developed small bowel cancer. A single exposure to DMH produced a significant increase in both the cAMP- and cGMP-PDE activities. Chronic exposure to DMH resulted in little apparent PDE changes in the small intestine until approx wk 20 at which time cAMP-PDE levels were similar to those measured in small bowel tumor cells. Ratios of cAMP and cGMP and cAMP-PDE and cGMP-PDE measured in the colon tissue following single and double DMH exposure were plotted against time. The measurements suggested that cyclic nucleotide content may be a reflection of tissue insult by an environmental toxicant. (19 Refs)

2. LOSS OF MUCOSAL SECRETORY COMPONENTS AND CHANGES IN GLYCOCONJUGATE COMPOSITION OF RAT COLONIC TUMORS (MEETING ABSTRACT).

Jacobs LR
Department of Internal Medicine, University of California, Davis, Davis, CA, 95616
Gastroenterology; 80(5,part2):1183 1981

The aim of this study was to characterize the changes in carbohydrate composition of epithelial cell membranes (ECM) and goblet cell mucus (GCM) in transitional mucosa and benign and malignant colonic neoplasms. Colonic tumors were induced in 16 rats with 16 weekly injections of dimethylhydrazine. All animals developed neoplasms within 24 wk. Fluorescein isothiocyanate (FITC) conjugated lectins were then used to stain tissue sections from normal rats and those with tumors. Control sections were incubated with 0.3 M of the binding inhibitor to confirm specificity. Binding to N-acetyl glucosamine was measured using Wheat germ agglutinin (WGA), mannose and glucose with Concanavalin A (Con A), galactose with Ricinus communis (RCA1), sialic acid with Limulus polyphemus (LPA) and fucose with Ulex europeus (UEA1). No specific changes in lectin binding could be consistently demonstrated to ECM or to transitional mucosa. The data show that GCM and its secretory elements were absent in colonic adenocarcinoma. In benign adenomas lectin staining of GCM GlcNac, Man, Glc, Gal and Fuc residues was diminished while that of NeuNAc was unchanged ; the decrease in GCM appeared to be greatest in the upper crypt. Thus alterations in GCM biosynthesis appear to correlate specifically with the degree of tumor malignancy, whereas in transitional mucosa goblet cell glyconconjugates appear normal. (no Refs)

3. GLYCOPROTEIN DEGRADING GLYCOSIDASES IN EXPERIMENTAL CANCER OF THE COLON (MEETING ABSTRACT).

Prizont R, Piatt K
Department of Medicine, Albuquerque Veterans Administration Medical Center, Albuquerque, NM
Gastroenterology; 80(5,part2):1255 1981

In this study, we have investigated the non-blood group degrading beta-Galactosidase (beta-Galase) and beta-N-Acetylglucosaminidase (beta-Glnase) in experimentally induced colonic cancer. Ten Wistar rats (ER) were injected for 10 wk with 25 mg/kg of 1,2 dimethyihydrazine (DMH) and fed a diet containing casein (20%), sucrose (50%), fat (5%) and cellulose fiber (5%). Another group of 10 rats (EHF) were similarly injected with DMH but the aforementioned diet was modified by both an increase in cellulose (to 15%) and a decrease in sucrose (to 40%). Two groups of rats, 6 each, were injected with buffer and served as controls for regular (CR) or high fiber (CHF) diets. Feces were collected, homogenized in saline and centrifuged to sediment the bacteria. Bacteria free supernatants were then used for analytical assays against p-nitro-phenylglycosides. When control and experimental animals were compared by diet (CHF vs EHF, CR vs ER), no significant differences in the enzyme levels were found. When animals were sacrificed 7 mo post-initial injection, significantly more tumors were recovered from large and small bowels of ER animals than were recovered from small bowels of EHF rats. This study suggests that high cellulose diets significantly decrease production of fecal non-blood group degrading glycosidases. (2 Refs)

4. BIOCHEMICAL AND CLINICAL EFFECTS OF SELENIUM ON DIMETHYLHYDRAZINE-INDUCED COLON CANCER IN RATS.

Jacobs MM, Forst CF, Beams FA
Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, Omaha, NE, 68105
Cancer Res; 41(11,part1):4458-4465 1981

The biochemical and clinical effects of selenium (Na2SeO3) on 1,2-dimethylhydrazine (DMH)-induced colon carcinogenesis in male Sprague-Dawley rats are presented. A 4-ppm selenium supplement to the drinking water was provided before, during, and after 20 weekly injections of 20 mg DMH per kg body wt. Immediately after the 20th DMH injection, part of the rats were sacrificed. The incidences of colon tumors in groups provided selenium before DMH, before and during DMH, and only during DMH treatment were reduced to 39, 43, and 36%, respectively. The incidence in the DMH only control was 63%. Other rats in all treated and control groups were maintained up to 5 mo post-DMH treatment. At 10-wk intervals throughout the study, selected blood and tissue components were analyzed. The following hematological changes correlated with DMH treatment. (a) Serum glutamic oxalacetic transaminase increased 2-fold (normal, 66 +-14 g/dl). (b) Serum alkaline phosphatase increased 24% (normal, 166 +-56 units/liter). (c) Serum protein decreased 14% (normal, 6.77 +-0.48 g/dl). (d) White blood count increased 2-to 3-fold (normal, 7.7 +-2.7 x 10(3)/cu mm). And (e) Hb decreased 67% (normal, 18.1 +-1.3 g/dl). The magnitude of these changes varies with each selenium treatment group and with each 10-wk analysis period. Provision of 4 ppm selenium doubled both liver and blood selenium levels compared to supplemented controls. The effects of selenium and DMH treatments on glutathione peroxidase and beta-glucuronidase activities and on sialic acid are presented. Possible mechanisms by which selenium protect against DMH-induced neoplasia are discussed. (Author abstract) (40 Refs)

5. MECHANISM OF FIBRE PROPHYLAXIS OF CHEMICALLY INDUCED COLONIC CARCINOMA IN THE RAT (MEETING ABSTRACT).

Harvey JS
Department of Surgery, University Hospital of Wales, Heath Park, Cardiff CF4 4XN, England
Eur Surg Res; 13(1):96 1981

The prophylactic effect of fiber on colonic carcinogenesis may be due to a reduction in energy intake rather than an effect on stool bulk and transit time. To test this hypothesis colon cancer was induced in rats whose diet was varied for energy intake as well as fiber intake. Sixty-two weanling rats were divided into four groups, matched for wt and rate of growth. All animals were given sc injections of dimethylhydrazine dihydrochloride (20 mg/kg at 10-day intervals for 150 days). The animals were housed and fed as follows until sacrificed at 170 days; group 1: normal diet ad lib, caged in fours; group 2: high fiber diet ad lib, caged in fours; group 3: high fiber diet ad lib, caged singly; group 4: normal diet restricted to the same energy, intake as group 3, caged singly. Adult mean wt with cancer incidences (in parentheses) were: group 1: 421 g (14/16); group 2: 391 g (14/16); group 3: 369 g (8/15); group 4: 358 g (10/15). There were no significant differences in cancer incidences between any of the groups taken individually and simply feeding fiber was not seen to offer any protection. Groups 1 and 2 combined had a significantly higher incidence of cancer than the smaller animals in groups 3 and 4 combined, which favors the hypothesis that any effect that fiber may have is related to cal restriction rather than to its mechanical effects in the bowel. (no Refs)

6. HIGH DIETARY CELLULOSE: PROTECTION AGAINST LARGE BOWEL CARCINOMA (MEETING ABSTRACT).

Prizont R, Piatt K
Division of Gastroenterology, Albuquerque Veterans Administration Medical Center, Albuquerque, NM
Gastroenterology; 80(5,part2):1256 1981

The effect of high cellulose diet in experimental carcinogenesis, was investigated in Wistar rats injected ip with 10 doses of 1,2 dimethylhydrazine (DMH). Ten experimental animals (ER) were fed a regular diet of casein (20%), sucrose (50%), fat (5%) and cellulose fiber (5%). A second group (EHF) received a similar diet modified by an increase of cellulose (to 15%) and a concomitant 10% decrease of sucrose. Two groups of 6 rats each were injected with buffer and used as animal controls on a regular or high fiber diet. When food consumption was measured, ER animals averaged 20.5 +/-0.3 g/day and EHF rats, 22.7 +/-0.3 g/day. In the same period of time, ER animals had significantly (p less than 0.005) lower fecal outputs than did EHF rats. Rats were sacrificed 7 mo after initial DMH injection. Conversely, 17 intestinal tumors were found in ER animals, which was significantly higher than the 4 recovered from EHF rats. Histological examination revealed that 15 of the 17 ER tumors were malignant (14 adenocarcinomas and 1 signet ring carcinoma). Only 2 of the EHF tumors were adenocarcinomas. The small intestine of ER rats contained 9 tumors (8 adenocarcinomas). The same area in EHF animals yielded 4 tumors (2 malignant). The large intestine of ER rats contained 8 neoplasms (7 malignant), but no benign or malignant tumors were found in the EHF large bowels. This study indicates that DMH injected rats fed a high cellulose diet develop significantly fewer intestine tumors. (1 Ref)

7. FAILURE OF DIETARY CELLULOSE FIBER TO PREVENT COLON TUMORS IN DIMETHYLHYDRAZINE (DMH)-TREATED RATS ON HIGH CHOLESTEROL DIETS (MEETING ABSTRACT).

Tempero MA, West W, Zetterman RK
Department of Internal Medicine, Veterans Administration Medical Center, Omaha, NE, 68105
Gastroenterology; 80(5,part2):1301 1981

A prior study has suggested that dietary fiber (cellulose) may decrease colon carcinogenesis in the DMH-induced rat model. We have evaluated the effect of dietary cellulose fiber on DMH-induced colon tumors in rats fed high cholesterol diets (a suspected co-carcinogen with DMH). Synthetic diets containing excess cholesterol and variable fiber content were fed to male Sprague-Dawley rats: Group I (0% fiber), Group II (5% fiber), and Group III (20% fiber). Half of each group received sc injections of DMH for 20 wk. Control rats received saline. All animals were sacrificed 1 wk after the last injection and blood obtained for cholesterol determination. Rat colons were inspected grossly and microscopically for invasive adenocarcinoma. Saline control animals were tumor free. No difference in either tumor incidence or number of tumors per affected rat colon was observed. Furthermore, the presence of dietary fiber did not alter serum cholesterol level supporting prior observations that cellulose fiber does not affect cholesterol metabolism. These findings suggest excess dietary cholesterol may diminish the protective effect of dietary fiber on DMH-induced colon tumors, possibly through an intraluminal mechanism. (1 Ref)

8. 1,2-DIMETHYLHYDRAZINE-INDUCED CHANGES IN HEPATIC, SMALL INTESTINAL, AND COLONIC MUCOSAL CYTOCHROMES P-450 AND B5 OF RATS FED CITRUS PULP OR WHEAT BRAN.

Smith-Barbaro P, Hanson D, Reddy BS
Naylor Dana Inst. for Disease Prevention, Valhalla, NY, 10595
Drug Metab Dispos; 9(5):487-488 1981

A 3-mo feeding study showed that dietary fiber and the carcinogen 1,2-dimethylhydrazine interacted to alter hepatic and extrahepatic levels of cytochromes P-450 and b5 in liver, and small intestine and colon mucosa of male F344 rats. (16 Refs)

9. EFFECT OF ANTIBIOTICS ON INCIDENCE OF RAT INTESTINAL TUMORS INDUCED BY 1,2-DIMETHYLHYDRAZINE DIHYDROCHLORIDE.

Goldin BR, Gorbach SL
Infectious Disease Service, Dept. Medicine, New England Medical Center Hosp., Tufts Univ. Sch. Medicine, 171 Harrison Ave., Boston, MA, 02111
JNCI; 67(4):877-880 1981

The intestinal microflora has been shown to influence the induction of chemical carcinogens responsible for intestinal tumors in animal models. For further exploration of this issue, male inbred F344 rats were administered a chemical carcinogen, 1,2-dimethylhydrazine dihydrochloride (DMH), for 20 wk, along with oral antibiotics, either tetracycline or erythromycin, to suppress the intestinal flora. Colon cancer incidence was lower in animals receiving antibiotics; 22% of the erythromycin-treated rats and 20% of the tetracycline-treated rats had colon tumors compared to untreated controls with a 74% tumor incidence (p less than 0.002). Tumors in the small intestine also decreased from an incidence of 48% in the control animals to an incidence of 27 and 7%, respectively, for the erythromycin- and tetracycline-treated rats. These findings suggested that the metabolic activity of the intestinal flora is related to cancer induction by DMH. (Author abstract) (23 Refs)

10. CANCER INDUCTION IN MICE WITH ACETALDEHYDE METHYLFORMYLHYDRAZONE OF THE FALSE MOREL MUSHROOM.

Toth B, Smith JW, Patil KD
Eppley Inst. Res. in Cancer and Allied Diseases, Univ. Nebraska Medical Center, Omaha, NE, 68105
JNCI; 67(4):881-887 1981

Acetaldehyde methylformylhydrazone (AMFH), which occurs up to 0.3% in one of the edible false morel mushrooms, Gyromitra esculenta, was administered to noninbred Swiss mice in propylene glycol in 52 weekly intragastric instillations as 100 ug/g body wt. The treatment induced tumors of the lungs, preputial glands, forestomach, and clitoral glands. The tumor incidences in these four tissues in treated females were 70, 0, 16, and 12%, respectively, whereas in the treated males they were 40, 90, 0, and 0%. The corresponding tumor incidences in the solvent control females were 26, 0, 0, and 0%, whereas in the solvent control males they were 22, 0, 0, and 9%, respectively. Histopathologically, the neoplasms were classified as adenomas and adenocarcinomas of the lungs; squamous cell papillomas and carcinomas, adenocarcinomas, undifferentiated carcinomas, angiosarcomas, and fibrosarcomas of the preputial glands; squamous cell papillomas and carcinomas of the forestomach; and squamous cell papillomas and carcinomas and keratoacanthomas of the clitoral glands. The study thus proves for the first time the tumorigenicity of AMFH. In view of these and earlier findings, the human population should abstain from consumption of Gyromitra esculenta. (Author abstract) (21 Refs)

11. STUDIES OF THE TUMORIGENIC POTENTIAL OF 4-SUBSTITUTED PHENYLHYDRAZINES BY THE SUBCUTANEOUS ROUTE.

Toth B, Nagel D
Eppley Inst., Univ. Nebraska Medical Center, Omaha, NE, 68105
J Toxicol Environ Health; 8(1/2):1-9 1981

Three groups of 50 male and 50 female Swiss mice, approx 6 wk of age, were given 26 weekly sc injections of 4-methylphenylhydrazine hydrochloride (4-MPH; 140 ug/g body wt), N'-acetyl-4-(hydroxymethyl)phenylhydrazine (AMPH; 500 ug/g). As a control, physiological salt soln (0.01 ml/g) was given. Over an observation period of 130 wk there was no significant difference in survival between treated and control groups. Two 4-MPH treated females developed soft tissue tumors at the injection site. Twelve 4-MPH-treated males developed soft tissue fibrosarcomas. In the AMPH study, no such tumors were seen in females while two males developed tumors at injection site (one fibrosarcoma, one angiosarcoma). Among controls two developed fibrosarcomas at injection site. The development of soft tissue tumors at injection sites of 4-MPH-treated mice was unexpected, since very few water-soluble carcinogens act locally. (25 Refs)

HETEROCYCLIC COMPOUNDS

12. MUTAGENICITY OF THE REACTION PRODUCTS OF L-ASCORBIC ACID AND L-TRYPTOPHAN.

Kanamori H, Morimoto K, Kinae N, Tomita I

Hiroshima Prefectural Institute of Public Health, Uzina-Kanda, Hiroshima 734, Japan

Yakugaku Zasshi; 101(7):596-604 1981

Glycine, dl-phenylalanine, l-tryptophan, and ammonia were allowed to react with l-ascorbic acid and d-glucose, in a 0.1M phosphate buffer (pH 7.0) at 37 C for 2 mo; the reaction mixtures were analyzed structurally and were tested for mutagenicity to Salmonella typhimurium TA 98 and TA 100 and to Bacillus subtilis (Ames test). Except for the mixture of l-ascorbic acid and ammonia, DNA-damaging effects were seen for reaction mixtures of l-ascorbic acid, but none were observed for reaction mixtures of d-glucose. Reaction mixtures of l-tryptophan and l-ascorbic acid were found to be DNA-damaging at day 8 after mixing, and the activity of the reaction mixture increased by mo 2, but DNA-damaging activity of this reaction mixture decreased after 2 mo. Following extraction of the reaction products of l-tryptop han and l-ascorbic acid with benzene and ethyl acetate and purification with silica-gel column chromatography and thin layer chromatography, mutagenic activity against S typhi TA 100 was observed for one fraction containing 1-(2-furyl)-9H-pyrido-[3,4-b]-indole with or without S-9 mixture and for 1-(2-furyl)-9H-pyrido[3,4-b]-indole carboxylic acid in the absence of the S-9 mixture. (15 Refs) (In JPN)

13. SPECIES DIFFERENCE IN N-HYDROXYLATION OF A TRYPTOPHAN PYROLYSIS PRODUCT IN RELATION TO MUTAGENIC ACTIVATION.

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Cancer Res; 41(11,part1):4518-4522 1981

Metabolic activation of a tryptophan pyrolysate, 3-amino-1-methyl-5H-pyrido[4,3-b]indole (Trp-P-2), in liver microsomes from rats, mice, hamsters, guinea pigs, and rabbits was studied to know whether N-hydroxylation is a common obligatory step for mutagenic activation of Trp-P-2. Among hepatic microsomes obtained from untreated animals, the highest activity of Trp-P-2 N-hydroxylase was observed in microsomes from hamsters, followed by those from guinea pigs, mice, and rabbits. In rats, the activity was low, and there was no appreciable difference between the sexes. The activity of Trp-P-2 N-hydroxylase in microsomes was increased by pretreating the animals with a polychlorinated biphenyl mixture. The induction was most profound in rats, and the activity was enhanced 257-fold, as compared to that of untreated animals. The activity was also enhanced in microsomes from polychlorinated biphenyl mixture-treated rabbits, mice, and hamsters, while the activity was increased only slightly in guinea pigs and was thereby lowest among microsomes from the polychlorinated biphenyl mixture-treated animals. In bacterial mutagenesis test systems using Salmonella typhimurium TA 98, the number of revertants induced by Trp-P-2 was increased in parallel with the microsomal ability of the N-hydroxylation. These results indicate that in all species examined N-hydroxylation is an essential metabolic step for mutagenic activation of Trp-P-2. (Author abstract) (32 Refs)

14. EFFECTS OF PHENOBARBITAL PRETREATMENT ON THE METABOLISM AND TOXICOKINETICS OF AFLATOXIN B1 IN THE RHESUS MONKEY.

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Toxicol Appl Pharmacol; 60(3):387-397 1981

Five male rhesus monkeys were treated with phenobarbital (PB: 15 mg/kg, 2 x/day) for 1 wk prior to administration of aflatoxin B1 (AFB1: 0.1-1.0 mg/kg, iv). PB pretreatment enhanced the in vitro conversion of AFB1 to aflatoxin Q1 and aqueous metabolites in monkey liver. Although PB did not appreciably alter the rate or vol of AFB1 distribution in vivo, it reduced plasma levels of total aflatoxin s, AFB1, and the toxic metabolite aflatoxin M1 (AFM1). Decreased AFM1 levels and increased levels of less toxic water-soluble metabolites were found in the urine of PB-treated monkeys. These findings demonstrated that increased hepatic AFB1 metabolism results in elimination and circulation of less toxic, less mutagenic, and highly excretable metabolites. (49 Refs)

15. EXPERIMENTAL RESEARCH ON THE CARCINOGENIC ACTIVITY OF EPICHLOROHYDRIN BY ORAL ADMINISTRATION IN MALE WISTAR RATS.

Kawabata A
Second Dept. Internal Medicine, Nara Medical Univ., Nara, Japan

Nara Igaku Zasshi; 32(3):270-280 1981

Carcinogenic activity of epichlorohydrin (E) administered in drinking water ad libitum to 72 male Wistar rats for 81 wk is reported. The rats were divided into four groups; Group 1 were given drinking water without E, Group 2 were given 375 ppm E in drinking water. Group 3 were given 750 ppm E in drinking water, and Group 4 were given 1,500 ppm E in drinking water. Following wk 81 of the experiment, various hematological analyses were performed in rats from each group, and the rats were sacrificed in order to histologically examine any resulting tumors. In Group 2 were observed macroscopically 5.6 +-8.4 tumor foci in the forestomachs, and 7/9 rats had hyperplasia of the gastric epithelium. In Group 3 were seen 9.9 +-12.8 tumor foci in the forestomachs; hyperplasia was noticed in 9/10 rats, papilloma in 1/10, and squamous cell carcinoma in 1/10. In Group 4 were seen 32.8 +-24.0 tumor foci in the forestomachs; hyperplasia was observed in 12/12 rats, papilloma in 7/12, and squamous cell carcinoma in 2/12. No tumors were observed in Group 1. Also, squamous cell carcinoma of the oral cavity was observed in 3/12 rats of Group 4, mesotheliomas were observed in 2/10 rats of Group 1, 2/9 in Group 2, 4/10 in Group 3, and 3/12 in Group 4. The results suggested that E had a direct carcinogenic effect on rats. (26 Refs) (In JPN)

16. MODIFICATION OF THE EFFECT OF DIPINE AND PHOTRINE IN A CULTURE OF HUMAN LYMPHOCYTES.

Batikian GG, Zalinian GG, Arutiunian RM
State Univ., Erevan, USSR

Tsitol Genet; 15(4):31-36 1981

The mutagenic effects of ethylenimine derivatives dipine and photrine were studied in cultured human lymphocytes. Addition of radioprotectors aminopropylaminoethylthiophosphoric acid and cystaphos reduced the yield of dipine- and photrine-induced mutations. (8 Refs) (In RUS)

17. 32P-LABELING TEST FOR DNA DAMAGE.

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Proc Natl Acad Sci USA; 78(10):6126-6129 1981

Covalent adducts formed by the reaction of DNA with chemical carcinogens and mutagens may be detected by a 32P-labeling test. DNA preparations exposed to chemicals known to bind covalentl y to DNA [N-methyl-N-nitrosourea, dimethyl sulfate, formaldehyde, beta-propiolactone, propylene oxide, streptozotocin, nitrogen mustard, and 1,3-bis(2-chloroethyl)-1-nitrosourea] were digested to a mixture of deoxynucleoside 3'-monophosphates by incubation with micrococcal endonuclease (EC 3.1.31.1) and spleen exonuclease (EC 3.1.16.1). The digests were treated with [gamma-32P]ATP and T4 polynucleotide kinase (ATP:5'-dephosphopolynucleotide 5'-phosphotransferase, EC 2.7.1.78) to convert the monophosphates to 5'-32P-labeled deoxynucleoside 3',5'-bis-phosphates. These compounds were then separated on polyethyleneimine-cellulose thin layers in ammonium formate and ammonium sulfate soln. Autoradiograms of the chromatograms obtained by this high-resolution procedure showed the presence of nucleotides derived from chemically altered, as well as normal, DNA constituents. Maps from DNA exposed to any of the chemicals used exhibited a spot pattern typical for the particular chemical. This method detected a single adduct in 10(5) DNA nucleotides without requiring that the compound under investigation be radioactive and thus provides a useful test to screen chemicals for their capacity to damage DNA by covalent binding. (Author abstract) (41 Refs)

INORGANIC AGENTS AND PARTICULATES INCLUDING FIBERS

18. THE CARCINOGENICITY OF BERYLLIUM.

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Environ Health Perspect; 40:101-105 1981

Studies of beryllium (Be) and some of its alloys and compounds have provided suggestive, but not conclusive evidence of carcinogenicity in humans. Malignant tumors of the lung and osteogenic sarcoma have been induced experimentally in rabbits, monkeys, and rats by Be metal, alloys, and compounds. Be was not mutagenic in bacteria, but induced morphological transformation in mammalian cell cultures and enhanced viral transformation of mammalian cells. Epidemiological evidence of increased cancer risk in humans is still inconclusive. Problems with data include possibly inappropriate comparisons, the questionable value of straight-line extrapolation of death rates, the possibility that short exposures may have a causal effect, and the failure to take smoking habits into account. Data warrant the presumption of hazard in occupational exposure to Be. Current Environmental Protective Agency recommended standards for max exposure in plants are an av 2 ug/cubic m (m3)/8-hr day with a max short exposure of 25 ug/m3. Neighborhood exposures are set at a max monthly concentration of 0.01 ug/m3. (60 Refs)

19. THE CARCINOGENICITY OF CHROMIUM.

Norseth T
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Environ Health Perspect; 40:121-130 1981

A review is presented of interactions of trivalent and hexavalent chromium with biological materials, environmental and occupational chromium exposure, epidemiological and experimental studies of chromium carcinogenicity, and in vitro studies of chromium mutagenesis. Further studies are needed to determine whether trivalent chromium causes cancer and whether soluble and slightly soluble hexavalent salts differ in carcinogenic potency. The importance of smoking in chromium carcinogenesis needs to be established, as does the identity of the specific compound responsible for cancer in workers exposed to chromate. (98 Refs)

20. CHRONIC INHALATION EXPOSURE OF HAMSTERS TO NICKEL-ENRICHED FLY ASH.

Wehner AP, Dagle GE, Milliman EM
Biology Dept., Battelle Pacific Northwest Lab., Richland, WA, 99352
Environ Res; 26(1):195-216 1981

Hamsters were chronically exposed to approx 70 ug/liter respirable nickel-enriched fly ash (NEFA) aerosol, approx 17 ug/liter NEFA, or approx 70 ug/liter fly ash (FA) for up to 20 mo. A control group received sham exposures. The NEFA particles of respirable size contained approx 6% nickel, compared to about 0.3% for FA. Five hamsters/group were sacrificed after 4, 8, 12, or 16 mo of exposure. An additional five hamsters/group were withdrawn from exposure at the same intervals for lifelong observations. Exposures to NEFA had no significant effect on body wt and life span of the animals although heavy deposits of NEFA in the lungs were demonstrated. However, lung wt of the high NEFA- and of the FA-exposed animals were significantly higher than those of the low-NEFA group and the controls, and mean lung vol were significantly larger for the high-NEFA group and the FA group than for the low-NEFA group and the controls. Dust was deposited (anthracosis) in the lungs of all exposed hamsters. Incidence and severity of interstitial reaction and bronchiolization were significantly higher in the dust-exposed groups than in the sham-exposed controls. The severity of anthracosis, interstitial reaction, and bronchiolization was significantly lower in the low-NEFA group than in the high-NEFA and FA groups. While two malignant primary thorax tumors were found in two hamsters of the high-NEFA group, no statistically significant carcinogenesis was observed. Of the exposure-related changes, only anthracosis decreased after withdrawal from exposure. Pulmonary nickel burdens after 20 mo of exposure suggest that the pulmonary clearance rate was slower in the high-NEFA group than in the low-NEFA group. (Author abstract) (29 Refs)

21. RECENT RESEARCH ON NICKEL CARCINOGENESIS.

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Environ Health Perspect; 40:131-141 1981

Nickel carcinogenesis research since 1975 is reviewed, with emphasis on new experimental techniques for studying carcinogenesis in vivo and in vitro. The subjects covered include epidemiologic studies, clinical investigations, carcinogenicity tests in animals exposed to nickel compounds by different administration routes, x-ray diffractometry and radiotracer studies of alpha-Ni3S2 metabolism, electron microscope studies of alpha-Ni3S2-induced tumors, cytogenetic and tumor transplantation studies, effects of nickel compounds on DNA synthesis, cell culture studies, bacterial mutagenicity tests, and effects of metals on viral and bacterial DNA polymerase. Prospects for future research on nickel carcinogenesis are summarized. (82 Refs)

22. THE CARCINOGENICITY OF ARSENIC.

Pershagen G
Dept. Environmental Hygeine, Karolinska Inst., Stockholm, Sweden
Environ Health Perspect; 40:93-100 1981

Assessment of arsenic (As) as a carcinogen is reviewed. As occurs widely in the environment, being found in various ores, coal, tobacco, pesticides, water, air, and foodstuffs such as marine fish and crustaceans, swine and poultry, as well as in industrial processes. Distinguishing between organic and inorganic As is important in determining carcinogenicity. Only inorganic As has so far been linked to cancer. Epidemiological studies have associated lung cancer with occupational exposure to As in pesticide workers, copper smelters, and vintners using pesticides. Skin cancer has been associated with exposure to As in drinking water in several reports. Neoplastic changes in the skin include Bowen's disease and basal and squamous cell carcinomas. Experimental studies in animals have not provided conclusive evidence of AsS carcinogenicity. Investigation of metabolism indicates that As may interfere with DNA repair mechanisms. Recommendations for future research are made. (101 Refs)

23. CHEMOPREVENTION OF MAMMARY TUMORIGENESIS BY A COMBINED REGIMEN OF SELENIUM AND VITAMIN A.

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Dept. Breast Surgery, Roswell Park Memorial Inst., Buffalo, NY, 14263
Carcinogenesis; 2(9):915-918 1981

The effect of combined administration of selenium (Se) and retinyl acetate (RA) was studied in female Sprague-Dawley rats with 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary gland tumors. DMBA was given intragastrically at 5 mg/wk for 3 wk. Starting 2 wk before initiation of DMBA administration, rats were fed a diet supplemented by Se (4 mg/kg) and/or RA (250 mg/kg) for 26 wk. Incidence of mammary gland tumors in rats exposed to DMBA alone was 90.0%, compared with 53.3% in rats treated with Se alone, 46.7% in rats treated with RA alone, 16.6% in rats treated with Se + RA for 28 wk, and 50.0% in rats treated with Se + RA-supplemented diet for only 18 wk. (32 Refs)

24. ROLE OF CADMIUM IN CARCINOGENESIS WITH SPECIAL REFERENCE TO CANCER OF THE PROSTATE.

Piscator M
Dept. Environmental Hygiene, Karolinska Inst., S-104 01 Stockholm, Sweden
Environ Health Perspect; 40:107-120 1981

Published data on possible carcinogenicity of cadmium (Cd)are reviewed. Injection of large doses of Cd induced sarcomas at the injection site and eventual testicular tumors in experimental animals. Low-dose long-term exposures of animals to Cd did not produce testicular or prostatic cancers. Epidemiological studies show increased deaths due to prostate cancer among cadmium-exposed workers. Insufficient data were obtained to indicate a dose-response relationship. Although cancer mortality varies among populations, the rate of small latent prostatic cancer is relatively constant. Prostate cancer rates appear related to factors including race, marital status, and dietary habits, all of which may affect hormonal levels. Heavy Cd exposures result in increased Cd in the prostate and testes and in reduced testosterone synthesis in experimental animals. High-level exposure to Cd may affect zinc interactions with hormone production, indirectly contributing to development of prostatic cancer. Cd does not appear to act directly on cells. Low exposure does not appear to cause prostatic cancer. (122 Refs)

25. METAL INTERACTIONS IN CARCINOGENESIS: ENHANCEMENT, INHIBITION.

Nordberg GF, Andersen O
Dept. Environmental Hygiene, Umea Univ., Umea, Sweden
Environ Health Perspect; 40:65-81 1981

The roles of metals in enhancing or inhibiting carcinogenesis are reviewed. Conclusive evidence of the carcinogenicity of arsenic has not yet been found, although some studies suggest it. Arsenic may act as a cocarcinogen. Selenium seems to be weakly mutagenic in bacteria and some mammalian cell cultures. Antitumor properties have been reported in experimental animals. Zinc is necessary as a trace element in the diet and may have anticarcinogenic effects. Nickel is strongly carcinogenic in experimental animals and humans. Its effects may be counteracted by manganese. Lead has not been confirmed as a carcinogen, but its presence in the environment warrants high priority research particularly on its effects in combination with other compounds. Chromium has been related to lung, and possibly stomach, cancer in man. Cadmium contributes to prostatic cancer and Leydig cell tumors. These effects can apparently be counteracted by zinc treatments. Carcinogenesis by benzo[a]pyrene, nitrosamines, and asbestos appear to be promoted by some metallic dusts. Further studies in vitro and in appropriate animal systems are urged. (155 Refs)

26. ROLE OF COBALT, IRON, LEAD, MANGANESE, MERCURY, PLATINUM, SELENIUM, AND TITANIUM IN CARCINOGENESIS.

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Environ Health Perspect; 40:143-161 1981

Experimental, clinical, and epidemiological studies of the carcinogenicity of cobalt, iron, lead, manganese, mercury, platinum, selenium, and titanium are reviewed. Sources of exposure to these metals and their mutagenic effects are discussed. Excess lung cancer mortality has been observed in hematite miners, but occupational exposure to the other metals is not associated with an increased cancer risk. Platinum coordination complexes used in cancer chemotherapy are electrophilic reactants and thus capable of cancer initiation. Cobalt oxide and cobalt sulfate produce injection site and renal tumors in animals, and both are mutagenic. Manganous acetylacetonate and dichlorodicyclopentadienyl titanium also give rise to injection site tumors, but only the latter is mutagenic. Mercury compounds do not appear to be carcinogenic, although some produce genetic damage. The mutagenicity and carcinogenicity of selenium have not been established. (142 Refs)

27. RELATION OF PARTICLE DIMENSION TO CARCINOGENICITY IN AMPHIBOLE ASBESTOSES AND OTHER FIBROUS MINERALS.

Stanton MF, Layard M, Tegeris A, Miller E, May M, Morgan E, Smith A
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JNCI; 67(5):965-975 1981

In 72 experiments, durable minerals in the form of particles of respirable size and of wide chemical and structural varieties were implanted in the pleurae of outbred female Osborne-Mendel rats for periods of more than 1 yr. The incidence of induced malignant mesenchymal neoplasms correlated well with the dimensional distribution of the particles. The probability of pleural sarcoma correlated best with the number of fibers that measured 0.25 um or less in diameter and more than 8 um in length, but relatively high correlations were also noted with fibers in other size categories having diameters up to 1.5 um and lengths greater than 4 um. Morphologic observations indicated that short fibers and large-diameter fibers were inactivated by phagocytosis and that negligible phagocytosis of long, thin fibers occurred. The wide variety of compounds used in these experiments suggested that the carcinogenicity of fibers depended on dimension and durability rather than on physicochemical properties. (Author abstract) (33 Refs)

28. FIBER CARCINOGENESIS: EPIDEMIOLOGIC OBSERVATIONS AND THE STANTON HYPOTHESIS.

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JNCI; 67(5):977-989 1981

A review of various animal and epidemiological studies which attempt to clarify the relationship between cancer and various natural and man-made fibers is presented The Wagner animal experiments such as those with various forms of asbestos demonstrated increased mesotheliomas with finer, rather than coarser fibers. After analysis of various experimental studies, it was concluded that after intrapleural inoculation of 37-man-made fibers, optimum correlation with mesothelioma was obtained with fibers less than 1.5 micron in diameter and greater than 8 micron. The Stanton hypothesis (which states that durable fibers, such as asbestos, within defined ranges of diameter and length can cause cancer irrespective of their physicochemical nature) is explored. Analysis of this hypothesis in relation to mesothelioma in humans is presented. Two epidemiological studies of outbreaks of disease related exposure to mineral fibers (one in South Africa, the other in Turkey) are discussed which could be used to integrate the Stanton hypothesis, which was confined to animals, with the Timbrell's aerodynamic criteria that relate human exposure and fibrous materials. Further occupational studies indicate the importance of defining dangerous parameters discussed and avoiding their man-made replication. (61 Refs)

29. MANIFESTATIONS OF CELLULAR IMMUNITY IN THE RAT AFTER PROLONGED ASBESTOS INHALATION. II. ALVEOLAR MACROPHAGE-INDUCED SPLENIC LYMPHOCYTE PROLIFERATION.

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Environ Res; 26(1):182-194 1981

The present study has shown that alveolar macrophages from asbestos-exposed rats (dusted macrophages) can induce the proliferation of autologous splenic lymphocytes (dusted lymphocytes) as well as the proliferation of syngeneic lymphocytes from control nonexposed rats (control lymphocytes). Significant lymphoproliferation did not occur when alveolar macrophages from control rats (control macrophages) were cocultured with control or dusted splenic lymphocytes for similar periods of time (72 or 96 hr). The activation of control lymphocytes by dusted macrophages was similar, in some respects, to the lymphoproliferative response evoked by sodium periodate-treated control macrophages, since both these reactions peaked at 72 hr and were abolished by treatment of the macrophages with the reducing agent, L-cysteine. This periodate-like response produced by dusted macrophages appears to result from aldehyde-like modifications on the macrophage cell membrane. L-Cysteine treatment did not, however, affect the blastogenic response induced by dusted macrophages on dusted lymphocytes, which peaked at 96 hr. Since the in vitro addition of crocidolite to cell cultures did not trigger lymphoproliferation, these collective findings suggest the expression of asbestos-related antigen-like determinants on the surface of dusted macrophages. We conclude that the proliferative reactions induced in splenic lymphocytes by dusted macrophages were a consequence of two different phenomena:a periodate-like effect (noted in control lymphocytes) and an effect produced by a putative asbestos-related, macrophage-associated antigen (observed in dusted lymphocytes). (Author abstract) (43 Refs)

30. SURGICAL AND PATHOLOGIC ASPECTS OF ASBESTOSIS.

Sasser WF, Bari WA
Dept. Surgery, St. John's Mercy Medical Center, 621 S New Ballas Rd., St. Louis, MO, 63141
South Med J; 74(10):1178-1181,1185 1981

We studied 12 patients with occupational exposure to asbestos to evaluate the pulmonary diseases that result from protracted exposure to this fibrogenic and oncogenic fiber. The spectrum of diseases includes diffuse interstitial fibrosis, bronchogenic carcinoma, and malignant mesothelioma. Cigarette smoking is found to be a cocarcinogen with asbestos. Because of the impairment of pulmonary function in thise patients, surgery plays a limited role in their management. (Author abstract) (13 Refs)

31. MUTAGENIC ACTIVITY IN DIESEL EXHAUST PARTICULATES.

Nachtman JP, Xiao-bai X, Rappaport SM, Talcott RE, Wei ET
Standard Oil Co. California, Richmond, CA, 94802
Bull Environ Contam Toxicol; 27(4):463-466 1981

The mutagenicity of chloroform eluates of diesel exhaust particulate extracts was examined by Ames test with or without S-9 mix. Exhaust eluates produced S-9-independent mutagenic activity of approx 480 revertants/100 ug of extract/plate. The addition of live enzymes decreased mutagenic activity. After reduction of the exhaust extract with sodium borohydride, the S-9-independent activity was greatly diminished. Addition of S-9 to the reduced sample revealed the presence of S-9-dependent mutagenic activity. Results suggest the presence of nitroarene mutagens in diesel exhaust particulates. (12 Refs)

32. MUTAGENIC AND CYTOTOXIC EVALUATION OF PLUTONIUM-244 (MEETING ABSTRACT).

Andrews TK, Samuel JE, Frazier ME
Biology Department, Pacific Northwest Laboratory, Richland, WA, 99352
In Vitro; 17(3):222 1981

The low specific activity of 244Pu enabled us to conduct a study using in vitro assays to determine the chemical mutagenicity and cytotoxicity of this metal. The effects of this isotope were compared to those of 238Pu and 239Pu to distinguish chemical effects from those caused by radiation. Mutagenicity was determined by the CHO-K1 (Chinese Hamster Ovary) assay, which measures forward mutation of the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus. No significant increase in mutation frequency was observed at media concentrations up to 5 ug/ml; however, this isotope was mutagenic at concentrations above 6 ug/ml. A clonal growth assay (VERO), developed at this laboratory, was employed to determine cytotoxicity. As a measure of toxicity, this assay uses the 50% relative plating efficiency concept (RPE 50) ie, concentration of test material that produces a plating efficiency which is 50% of the control value. Concentration-response curves with the VERO growth assay show that 244Pu has an RPE 50 of 0.12 ug/ml, ranking it with the more toxic metals, ie, V greater than Cr greater than Ru greater than 244Pu greater than Cd greater than Hg. (no Refs)

AMIDES, CARBAMATES AND UREAS

33. INDUCTION OF GAMMA-GLUTAMYL TRANSPEPTIDASE POSITIVE FOCI IN RAT LIVER BY PYROLYSIS PRODUCTS OF AMINO ACIDS.

Tamano S, Tsuda H, Tatematsu M, Hasegawa R, Imaida K, Ito N
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Gan; 72(5):747-753 1981

The activities of pyrolysis products for initiating or promoting preneoplastic lesions were tested. In experimental series I, N-2-fluorenylacetamide (2-FAA) was used as a initiator or a promoter and 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1), 3-amino-1-methyl-5H-pyrido[4,3-b]indole (Trp-P-2), 2-amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole (Glu-P-1) or 2-aminodipyrido[1,2-a:3',2'-d]imidazole (Glu-P-2) was administered at a fixed dose and for the same period in the initiation stage or the promotion stage. Animals were subjected to partial hepatectomy or treated with carbon tetrachloride (CCl4) to increase the induction of gamma-glutamyl transpeptidase (gamma-GT) positive foci. Trp-P-1 and Glu-P-2 administered in either the initiation or promotion stage significantly increased the induction of gamma-GT positive foci (p less than 0.001). Glu-P-1 increased the induction of gamma-GT positive foci (p less than 0.001) when administered in the initiation stage but it was not effective when administered during the promotion stage. In experimental series II, animals were given a single dose of these chemicals at one of the three different dose levels with partial hepatectomy and then were fed with 2-FAA and given a single dose of CCl4. Trp-P-1, Glu-P-1 and Glu-P-2 caused dose-dependent inductions of gamma-GT positive foci. (Author abstract) (14 Refs)

34. RECENT CONCEPTS OF INITIATION AND PROMOTION IN CARCINOGENESIS.

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Am J Pathol; 105(1):3-9 1981

This review deals with premalignant liver lesions in rats fed N-2-acetylaminofluorene (AAF) or diethylnitrosamine (DEN), DNA alterations in premalignant lesions, and cellular responses to skin tumor promoters such as tetradecanoylphorbol acetate (TPA). Rats fed four cycles of AAF exhibited persistent hepatic nodules having increased mitotic activity and altered DNA. Similarly, premalignant lesions induced by DEN and phenobarbital showed an increase in altered DNA, which paralleled the increase in risk of hepatoma. The broad effects of tumor promotion consist of the induction of proliferation of an initiated cell population and the appearance of aggregates of altered cells. Tumor promoters such as TPA heighten the mitotic responses in these cells and eventually induce epigenetic programmatic alterations. (38 Refs)

35. POTENCY OF SOME CARBAMATES AS MULTIPLE TISSUE SISTER CHROMATID EXCHANGE INDUCERS AND COMPARISON WITH KNOWN CARCINOGENIC ACTIVITIES.

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Cancer Res; 41(11,part1):4489-4492 1981

The ethyl, ethyl N-hydroxy, isopropyl, and methyl esters of carbamic acid were examined for their abilities to induce sister chromatid exchanges (SCEs) in alveolar macrophages, bone marrow, and regenerating liver cells of C57BL/6J x DBA/2J F1 mice. The relative potencies in inducing SCE, ethyl greater than ethyl N-hydroxy- greater than isopropyl, paralleled previously described activities for induction of lung adenomas in strain A mice. The noncarcinogenic methyl carbamate was inactive in the SCE assay. Relative to bone marrow, regenerating liver and alveolar macrophage cells demonstrated increased susceptibility to carbamate-induced SCE. Of all carbamates studied, only the directly active compound, ethyl N-hydroxycarbamate, produced distinctly different responses in extrahepatic tissues of hepatectomized and intact mice. In intact mice, SCE levels induced by ethyl carbamate in bone marrow and alveolar macrophage cells were not significantly different whether assay followed the last of 12 (3x weekly) serial injections of 2.2 mmol/kg each or after a single injection of 2.2 mmol/kg. Linear regression relationships of log ethyl carbamate versus log SCE or log adenoma response were found to be parallel with the two assays having similar sensitivities. (Author abstract) (21 Refs)

36. CHEMICAL CARCINOGENESIS IN THE RAT: COMMON MODE OF ACTION OF CARCINOGENS AT THE CHROMOSOME LEVEL.

Sugiyama T, Ueda N, Maeda S, Shiraishi N, Goto-Mimura K, Murao S, Chattopadhyay SC

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JNCI; 67(4):831-839 1981

The chromosomal distribution of chromosome aberrations (CA) and sister chromatid exchanges (SCE) induced by various chemical carcinogens such as 7,12-dimethylbenz[a]anthracene, 7,8,12-trimethylbenz[a]anthracene, 1-butyl-1-nitrosourea, urethan, 4-nitroquinoline 1-oxide, 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide, and the antineoplastic compound mitomycin C was studied with the use of noninbred Long-Evans male rat bone marrow cells in vivo and in vitro. The CA and SCE induced by these structurally different chemicals were distributed in similar pattern among and along chromosomes when the chemicals were given a short time (6 hr) before the metaphase cells were harvested. The specific distribution pattern of chemically induced CA and SCE along chromosomes was attributed to the late DNA replication of the vulnerable chromosome regions. Conversely, x-ray-induced CA were distributed more randomly. Thus the different chemical carcinogens were shown to exert a similar genetic effect at the chromosome level. (Author abstract) (38 Refs)

AMINO ACID ANALOGS AND MODIFIED NUCLEIC ACID CONSTITUENTS

37. BLOCKING BY THE CARCINOGEN, L-ETHIONINE, OF SOS FUNCTIONS IN A TIF-1 MUTANT OF ESCHERICHIA COLI B/R.

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Cancer Res; 41(11,part1):4382-4385 1981

In Escherichia coli, DNA damage by carcinogenic agents results in the coordinate expression of a diversity of functions (SOS functions), many of which are thermally inducible without any damage to DNA in a tif-1 mutant. These include prophage induction, filamentous growth, and an error-prone DNA repair activity, which is responsible for UV-induced mutagenesis. Ethionine causes hepatic carcinoma in rats after prolonged feeding but is not a mutagen in the Ames test. The present study shows that 10 mM ethionine prevents the thermal induction of lambda-prophage in a tif-1 derivative of E. coli. The enhancement of mutation, which normally occurs at high temperature after a low dose of UV light, is also blocked by ethionine. Ethionine does not block, to any appreciable extent, the incorporation of radioactive precursors into RNA, DNA, or protein. (Author abstract) (30 Refs)

38. STRUCTURALLY DIVERSE HEPATOCARCINOGENS IN VITRO INDUCE DRUG RESISTANCE IN RAT HEPATOCYTES WHEN TESTED IN VITRO (MEETING ABSTRACT).

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Br J Cancer; 43(5):731 1981

Carcinogen-altered cells have generally been shown to be more resistant to the toxic effects of carcinogens than normal cells. It was therefore reasoned that the marked resistance of human hepatocellular carcinoma to cytotoxic chemotherapy might also be due to a carcinogen-induced phenotypic change in hepatocytes, resulting in an increased resistance to both carcinogen- and chemotherapy-mediated cytotoxicity. Male F344 rats were fed a basal diet and given aflatoxin B1 (AFB1) 30 ug daily ip or a basal diet containing either ethionine or 3'-methyl-4-dimethylaminoazobenzene. Rats were sacrificed weekly and their hepatocytes were placed in primary monolayer culture. Following a 3 hr attachment hepatocytes were exposed for 24 hr to Adriamycin (1.8x10-4M) cycloheximide (7x10-3M) or AFB1 (10-6M). Resistance was defined as the percentage of attached cells excluding trypan blue compared to untreated controls. Each of the 3 carcinogens induced greater than 50% resistance to AFB1 in the isolated hepatocytes after one wk, and comparable resistance to cycloheximide and Adriamycin after 4 wk. Hepatocytes from normal rats did not survive these concentrations of test drugs. In vivo, 3 different hepatocarcinogens induced marked resistance in rat hepatocytes to the potent carcinogen AFB1, as well as to the cytotoxic drug Adriamycin, using an in vitro assay, several mo before the appearance of hepatocellular carcinoma. Clinical drug resistance may be an early carcinogen-induced phenotype in primary tumors. (3 Refs)

39. CARCINOMA OF THE PANCREAS IN AZASERINE-TREATED RATS.

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Am J Pathol; 105(1):94-96 1981

Pancreatic carcinomas were induced in Wistar and Lewis rats by azaserine. Tumors in early stages were characterized by atypical acinar cell nodules. Histologic types included acinar cell adenocarcinoma, undifferentiated carcinoma, microadenoma, and duct- and cyst-like carcinomas. Tumors have been maintained by serial transplantation. Comparison with human disease is made. (14 Refs)

ALIPHATIC HALOGEN COMPOUNDS

40. ROLES OF 2-HALOETHYLENE OXIDES AND 2-HALOACETALDEHYDES DERIVED FROM VINYL BROMIDE AND VINYL CHLORIDE IN IRREVERSIBLE BINDING TO PROTEIN AND DNA.

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Cancer Res; 41(11,part1):4391-4398 1981

The metabolism of [1,2-14C]vinyl bromide (VBR) to products irreversibly bound to DNA and protein was examined in rat liver microsomes, reconstituted cytochrome P-450 systems, and isolated hepatocytes. A role for cytochrome P-450 was confirmed using inhibition and reconstitution experiments. The major form of cytochrome P-450 involved in VBR metabolism does not appear to be either of the major isozymes induced by phenobarbital or beta-naphthoflavone, as determined by induction, reconstitution, and antibody inhibition studies. 2-Bromoethylene oxide and 2-bromoacetaldehyde, suspected metabolites of VBR, were synthesized and found to be substrates for rat liver epoxide hydrolase and equine liver alcohol dehydrogenase, respectively. These enzymes were used to probe the roles of the two possible metabolites in the irreversible binding of products of VBR to protein and DNA. Alcohol dehydrogenase was more effective than epoxide hydrolase in inhibiting the binding of VBR metabolites to protein in microsomal incubations. Epoxide hydrolase was effective in inhibiting the binding of VBR or vinyl chloride metabolites to calf thymus DNA added to such systems, but alcohol dehydrogenase was not. Similar results were obtained for binding of VBR metabolites to DNA in a reconstituted enzyme system. Reduced glutathione blocked nonenzymatic binding of 2-bromo[1,2-14C]acetaldehyde to protein but not DNA. Binding of vinyl chloride and VBR metabolites to protein was blocked by reduced glutathione, but binding to DNA was not. These results are consistent with the view that 2-haloethylene oxides are the major alkylating agents bound to DNA, and 2-haloacetaldehydes are the major alkylating agents bound to proein in these experimental systems. Studies with labeled 2-bromoacetaldehyde indicate that the slow kinetics of DNA binding by this compound is responsible in part for this phenomenon. Studies with isolated rat hepatocytes suggest that a significant portion of the total and reactive metabolites are able to leave these cells. In these systems, binding of metabolites of vinyl chloride to DNA outside the hepatocytes could be partially blocked by epoxide hydrolase or by alcohol dehydrogenase, implying that, as targets farther away from sources of reactive species are considered, the stabilities of these species become more important for reaction with nucleophilic sites. (Author abstract) (36 Refs)

41. CHARACTERIZATION OF THE HEPATIC DNA DAMAGE CAUSED BY 1,2-DIBROMOETHANE USING THE ALKALINE ELUTION TECHNIQUE.

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Carcinogenesis; 2(9):839-844 1981

Hepatic lesions induced by 1,2-dibromoethane (EDB: 25-75 mg/kg, ip) in male Swiss Webster mice were assessed by a modified alkaline elution assay. The major changes were use of 47-mm diameter filters and a microfluorometric technique to quantify the DNA. EDB administration caused a dose-dependent increase in DNA strand breaks. Allowing the DNA sample to remain on the filter in the presence of pH 12.3 buffer facilitated the conversion of alkali-labile sites to strand breaks detectable by the alkaline elution technique. To determine the presence of DNA cross-linking after EDB exposure, one-half of the hepatic nuclei were x-irradiated (200 rads) at 0 C. No EDB-induced DNA-DNA or DNA-protein cross-links were detected. This method may be useful for studying the nature of DNA damage induced by in vivo carcinogens. (22 Refs)

42. MODIFICATION OF HEPATOTOXIC EFFECT OF HALOGENATED HYDROCARBONS ON PARTIALLY HEPATECTOMIZED RATS.

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Toxicol Eur Res; 3(4):197-200 1981

The effect of hepatectomy on the hepatotoxic effect of halogenated hydrocarbons was studied. Male rats received po administration of chloroform or carbon tetrachloride at a single dose of 500 mg/kg, 3 days prior to or after the partial hepatectomy. The hepatotoxic effect of the toxins was modified in a different manner according to the time of the hepatectomy. In the animals hepatectomized 3 days after the hepatotoxin administration, histological changes of the liver were similar to those of the non-hepatectomized rats, except with an increase in the activity of GOT and GPT. On the contrary, in the animals hepatectomized 3 days prior to hepatotoxin adminstration, the toxic effect of the chemicals was less enhanced than in the non-hepatectomized animals. (Author abstract) (12 Refs) (In FRE)

43. HEALTH RISKS FROM VOLATILE HALOGENATED HYDROCARBONS?

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Sci Total Environ; 20(2):171-189 1981

Human exposure to volatile halogenated hydrocarbons (VHH) and associated risks to health are reviewed. VHH are found in drinking water, air, and food. In West Germany the daily av burden for the most important VHH is in the range 0.1-1 ug/kg/day. However, many additional burdens of VHH which are not included in mean values of body-burden include occupational exposure, contaminated ground water, ingestion of contaminated fish, disinfection sol residue on infant feeding utensils, and ingestion of chloroform in swimming pools. Epidemiologic data reveal the carcinogenicity of VHH in man. Animal studies and in vitro studies support the hypothesis that VHH are carcinogenic and mutagenic in animals. Extrapolation of experimental findings to man and extrapolation from the necessary high doses used in bioassay to the substantially lower quantities found in the environment are discussed. The use of VHH in open systems in industry, food production, households, etc, should be minimized by the use of appropriate substitutes, better and stricter regulations, and appropriate control. (62 Refs)

POLYHALOGENATED RING COMPOUNDS INCLUDING INSECTICIDES

44. DNA METHYLATION AND METHYLASE LEVELS IN NORMAL AND MALIGNANT MOUSE HEPATIC TISSUES.

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Carcinogenesis; 2(9):873-878 1981

DNA methylation levels (expressed as the percentage of 5-methylcytosine relative to total cytosines) were measured in normal mouse liver, primary hepatocellular carcinomas (PHCs) in male C3H mice, PHCs induced in male C7Bl/6N mice by chlordane, N-acetylaminofluorene, or 3'-methyl-4-dimethylaminoazobenzene, and spontaneous and chemically induced PHCs in male (C7BL/6H x C3H/HeN)F1 (B6C3) mice. All tumors demonstrated an undermethylation of their genomes, compared with normal livers of age-matched controls. The undermethylation was not due to inactivation of or deficiency in DNA methylase activity, since enzyme levels in tumor nuclei were higher than background levels. The possibility that aberrations in DNA methylation are involved in the transformation of normal differentiated cells to neoplastic cells is discussed. (57 Refs)

45. DISTRIBUTION OF CYCLIC 3',5'-PHOSPHODIESTERASE, MONOAMINE OXIDASE AND BETA-GLUCURONIDASE IN LIVER TUMOURS INDUCED BY TECHNICAL GRADE HEXACHLOROCYCLOHEXANE IN INBRED SWISS MICE.

Bhatt DK, Nigam SK, Lakkad BC, Aravinda Babu K, Karnik AB, Thakore KN, Kashyap S K, Chatterjee SK
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Indian J Exp Biol; 19(7):625-629 1981

Male inbred Swiss mice were fed 500 ppm technical grade hexachlorocyclohexane (BHC) in their diet for 8 mo after which time the distribution of cyclic 3',5'-phosphodiesterase (cPDE), monoamine oxidase (MAO), and beta-glucuronidase (bGLU) was investigated. There was no difference in mortality between the experimental and control groups. All treated animals developed hepatocellular carcinomas. The distribution of cPDE in the tumor increased, particularly in large droplet-like cytoplasmic activity. In control animals, the MAO activity in the liver was homogeneous in all areas. MAO activity in the tumor was mainly cytoplasmic and nuclei remained unstained. bGLU activity decreased considerably in tumors and nontumor parts of treated animals compared to controls. bGLU activity was very strong in vacuoles. (24 Refs)

46. HISTOCHEMICAL CHANGES IN ATPASE DISTRIBUTION DURING HEXACHLOROCYCLOHEXANE INDUCED HEPATOCARCINOGENESIS IN INBRED SWISS MICE.

Bhatt DK, Nigam SK, Aravinda Babu K, Lakkad BC, Karnik AB, Thakore KN, Kashyap SK, Chatterjee SK
Natl. Inst. Occupational Health (ICMR), Meghani Nagar, Ahmedabad 380 016, India
Indian J Exp Biol; 19(7):621-624 1981

The distribution of ATPase at gross and cellular levels during hepatocarcinogenesis induced by technical grade hexachlorocyclohexane (BHC) in male inbred Swiss mice was investigated. The animals received 500 ppm BHC in diet for 2, 4, and 6 mo. After 2 mo, the periportal areas in the liver were intensely stained in the animals fed BHC compared to central vein areas. In control preparations, hepatocytes in central and periportal areas were homogeneously stained. Hepatocytes in the BHC animals in the central vein area showed strong activity on the bile canaliculi and plasma membranes. After 4 mo exposure to BHC, neoplastic nodules showed marked decrease in ATPase activity. The plasma membrane and bile canaliculi had diminished ATPase activity. After 6 mo exposure, the liver tumors which had developed showed intense ATPase activity in the plasma membrane of tumor cells and considerably diminished or absent activity on the nucleus. (24 Refs)

47. PHENOXY ACIDS: A BRIEF REVIEW OF THE POSSIBLE HYGIENIC EFFECTS.

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Lakartidningen; 78(34):2861-2862 1981

Recent studies on the hygienic effects of phenoxy acids used as pesticides are reviewed. 2,3,7,8-Tetrachloro-dibenzo-p-dioxin, occurring in a small amount as impurity in (2,4,5-trichlorophenoxy)acetic acid (2,4,5-T), was found to be a carcinogen and possibly a promoter in experimental animals. Small quantities of other dioxins, eg, tetrachloro-p-dioxin, were found in (2,4-dichlorophenoxy)acetic acid (2,4-D). Increased incidence of tumors and malformations due to 2,4,5-T was found in mice, and increased incidence of lymphosarcoma and tumors of endocrine organs was found in rats treated with 2,4-D. The mutagenicity tests of the phenoxy acids and dioxins yielded contradictory results. No carcinogenic effect of 2,4-D and 2,4,5-T was demonstrated in some animal experiments. Epidemiological studies showed a link between soft-tissue sarcoma and lymphosarcoma and exposure to phenoxy acids. Other epidemiological studies showed no relationship. Yet, a link between cancer and exposure to 2,4,5-T seems to exist in the light of experimental and epidemiological data. (10 Refs) (In SWE)

48. PHENOXY ACIDS, CHLOROPHENOLS, AND CANCER.

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Lakartidningen; 78(34):2862-2863 1981

Recent studies on the carcinogenic effects of phenoxy acids and chlorophenols in occupationally exposed subjects are reviewed. Relationship between exposure to phenoxy acids and chlorophenols and malignant mesenchymal soft-tissue tumors was found in two case-control studies in Sweden. Increased risk of malignant lymphoma was also demonstrated in another study. Malignant lymphoma, acute leukemia, and malignant mesenchymal soft-tissue tumors were found at significantly increased incidence among workers exposed to (2,4,5-trichlorophenoxy)acetic acid 2,4,5-trichlorophenol, and the impurity 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD). TCDD was found to induce malignant mesenchymal soft-tissue tumors, and 2,4,6-trichlorophenol caused increased incidence of hepatocellular carcinoma, malignant lymphoma, and leukemia in rats. (15 Refs) (In SWE)

BENZENE DERIVATIVES

49. BENZENE INDUCED BONE-MARROW INSUFFICIENCY.

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Trends Pharmacol Sci; 2(10):265-267 1981

History, clinical and experimental findings, and cytogenetic effects of benzene are discussed in relation to benzene-induced bone marrow insufficiency. A high level of benzene exposure has been associated with high incidence of pancytopenias and bone marrow dysplasia. A small number of these cases may develop into leukemia, usually of the acute myelogenous variety. The overall incidence of malignant disease in highly exposed individuals is approx double that of the general population. The risk of lower levels of exposure is a matter of epidemiological debate. Experimental studies indicate that benzene induces hematopoietic failure at the level of the maturing progenitor cell, beyond the pluripotent stem cells. Such failure is expressed by progressive dysplastic changes in bone marrow and peripheral blood. In addition, several lines of investigation have indicated a deranged interaction between stem cells, progenitor cells, and the regulating microenvironment. Unlike the situation in humans, no malignancy has been induced by benzene in vivo in animals. Perhaps in humans additional toxicity is afflicted on the hematopoietic stem cell. (10 Refs)

50. CARCINOGENICITY OF BENZYL CHLORIDE, BENZAL CHLORIDE, BENZOTRICHLORIDE AND BENZOYL CHLORIDE IN MICE BY SKIN APPLICATION.

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Gan; 72(5):655-664 1981

The carcinogenicity of benzyl chloride (BYC), benzal chloride (BAC), benzotrichloride (BTC) and benzoyl chloride (BOC), which were suspected as causative agents of lung cancer and maxillary malignant lymphoma of workers employed in factories producing BOC, was examined by skin applications in female ICR mice. After rather high dose exposure, BTC exhibited leukemogenic and pulmonary tumorigenic activities as well as potent dermal carcinogenic activity. After administration of the chemicals at the dose of 2.3 ul/animal, twice a wk for 50 wk, BTC induced 68% incidence of skin cancers and 58% incidence of pulmonary tumors (including 10% of lung carcinomas) within 399 days. Incidence of skin cancers was 58% for BAC, 15% for BYC and 10% for BOC within 560 days. Considering the extent of possible exposure of the workers to these chemicals in the working environment and the carcinogenic potency of the chemicals tested, it can be concluded that BTC was very probably responsible for causing the cancers seen in the workers employed in manufacturing BOC. (Author abstract) (16 Refs)

51. THE METABOLISM AND EXCRETION OF STYRENE OXIDE-GLUTATHIONE CONJUGATES IN THE RAT AND BY ISOLATED PERFUSED LIVER, LUNG AND KIDNEY PERFUSIONS.

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J Pharmacol Exp Ther; 219(1):35-41 1981

The metabolism and excretion of styrene oxide (SO)-glutathione conjugates (SO-GSH) were studied in the intact rat by isolated perfusion techniques in rat lung, liver and kidney. Styrene, or its metabolite, SO, constitutes a potential biohazard, since the latter is a known mutagen. The experiments demonstrated that the rat is capable of rapid conversion of SO-GSH to various derivative metabolites, and of rapid excretion of all SO thioether conjugates. (22 Refs)

52. EFFECT OF PHENOBARBITAL PRETREATMENT ON THE TOXICITY AND METABOLISM OF 2,4-DIAMINOANISOLE.

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Biochem Pharmacol; 30(19):2715-2718 1981

The effects of phenobarbital (PB) on the acute toxicity, macromolecular binding, disposition, and metabolism of 2,4-diaminoanisole (2,4-DAA) were studied in young male Fischer rats. At 5 and 24 hr after ip injection of [14C]-2,4-DAA, the highest concentration in control and PB-pretreated animals occurred in the kidney. Lower levels were found in the liver, spleen, lung, heart, and testis, respectively. The higest concentration of 2,4-DAA bound to tissue macromolecules was found in the kidney, followed by the liver, spleen, lung, heart, and testis, respectively. Concentrations of bound materials at 24 hr were approx half of those observed at 5 hr. Pretreatment with PB significantly increased binding, but only in the liver and kidney and not in other organs. In control rats, who received equal vol of NaCl and [14C]-2,4-DAA, 31% of the 14C dose was found in the urine in 5 hr, and 69% by 24 hr. In PB-pretreated rats, the rate of excretion of radioactivity was somewhat faster than that of the control animals: 42% of the radioactivity was in the urine at 5 hr. No difference in the excretion of total radioactivity or of the radioactivity in each fraction was observed between the PB-pretreated and control groups at the 24 hr period. The high pressure liquid chromatography separation of the five known metabolites of 2,4-DAA in control and PB-pretreated rats is described. The acute toxicity of 2,4-DAA was increased by PB treatment as evidenced by a change in the LD50 dose from 116 mg/kg to 97 mg/kg in the PB-pretreated rats. The mechanism and implications of the PB-related effects on 2,4-DAA metabolism are discussed. (14 Refs)

DRUGS, COSMETICS, DETERGENTS AND OTHER COMMERCIAL MATERIALS

53. MUTAGENICITY, TUMORIGENICITY, AND ELECTROPHILIC REACTIVITY OF THE STEREOISOMERIC PLATINUM(II) COMPLEXES OF 1,2-DIAMINOCYCLOHEXANE.

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Cancer Res; 41(11,part1):4368-4377 1981

Without external activation, cis- and trans-dichlorodiammineplatinum(II) and the cis, trans(-), and trans(+) forms of dichloro-1,2-diaminocyclohexaneplatinum(II) (DDCP) and sulfato-1,2-diaminocyclohexaneplatinum(II) (SHP) showed a 400-fold range of mutagenicity for Salmonella typhimurium TA100 and TA98; they were 2 to 10x more mutagenic for strain TA100 than for strain TA98. With strain TA100, trans-DDP was less than 0.5% as mutagenic as the cis isomer, which produced 180 revertants/nmol. For the diaminocyclohexane complexes, mutagenic activity was strongly dependent on the stereoisomer of the diaminocyclohexane in the complex. Thus, with strain TA100, the trans(+) forms of DDCP and SHP produced 220 and 66 revertants/nmol, respectively, while the cis- and trans(-) isomers induced only 10 and 5% as many revertants as the trans(+) forms. The SHP complexes were the most reactive toward DNA and produced a greater reduction in the transforming activity of Bacillus subtilis DNA after 3-hr reaction times than did the DDP or DDCP complexes. With 20-hr reaction times, all of the platinum complexes showed similar extents of reaction with DNA and caused approx equal losses of transforming activity. The stereoisomeric form of the diaminocyclohexane ligand of the DDCP or SHP complexes did not affect either the reactivity of the complex with DNA or its ability to reduce the transforming activity of DNA. Significant increases in the number of lung adenomas in A/J mice were induced by multiple ip injections of cis-DDP and each of the DDCP and SHP complexes (total doses, 21 to 108 umol/kg body wt). Similar treatments with cis-DDP caused a significant increase in the number of skin papillomas in female CD-1 mice given promoting treatments with croton oil; the DDCP and SHP complexes had little or no activity in this system. At these levels, trans-DDP was not active for the induction of either lung adenomas or skin tumors. With the systems used for this study, the mutagenicities and tumorigenicities of the platinum(II) complexes did not correlate with their reported antitumor activities. Further studies appear warranted to determine whether there may be effective antitumor platinum (II) complexes that are not strongly mutagenic or carcinogenic. (Author abstract) (56 Refs)

54. TOXICITY, INTERSTRAND CROSS-LINKS AND DNA FRAGMENTATION INDUCED BY 'ACTIVATED' CYCLOPHOSPHAMIDE IN YEAST.

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Chem Biol Interact; 37(1):123-140 1981

Treatment of yeast cells with 4-hydroperoxy-cyclophosphamide (4-OOH-CP), the chemically activated form of cyclophosphamide, results in cell killing, induction of DNA interstrand cross-links and DNA fragmentation. Toxicity of 4-OOH-CP is greatly influenced by the cell's capacity of DNA dark-repair: genetic blocking of non-epistatic pathways of DNA repair results in an increase of sensitivity by several orders of magnitude. DNA primary lesions have been measured using a haploid, excision deficient, dTMP-uptaking mutant of S cerevisiae. In this strain, a significant extent of DNA cross-linking can already be observed at a survival of 88%. At a concentration of 100 nmol/ml 4-OOH-CP, renaturability of DNA increases up to 12 hr of drug exposure and drops to lower values upon further incubation. In contrast to the time course of renaturability, DNA double-strand breakage is seen at later stages of drug treatment and continuously increases as a function of incubation time. Whereas inactivation of cells and induction of strand breakage continue upon postincubation of cells, comparable effects are much less pronounced for DNA renaturability. (Author abstract) (53 Refs)

55. COMPARATIVE STUDY ON THE EFFECTS OF CYCLOPHOSPHAMIDE ON YEAST IN VITRO AND IN THE HOST-MEDIATED ASSAY: DNA DAMAGE AND BIOLOGICAL RESPONSE.

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Chem Biol Interact; 37(1):141-154 1981

Cyclophosphamide (CP), whether applied in its chemically activated form as 4-hydroperoxy-cyclophosphamide in vitro or in the host-mediated assay using rats, exhibits toxic and mutagenic effects on excision deficient yeast cells. The expression of these effects is examined during a prolonged postincubation in buffer and compared with the ability of activated CP to induce interstrand cross-links and DNA fragmentation. At comparable doses, we observe a close similarity of biological and biochemical effects in either test system. (Author abstract) (23 Refs)

56. EVALUATION OF EXPERIMENTAL PARAMETERS IN AN S9/HUMAN LEUKOCYTE SCE TEST WITH CYCLOPHOSPHAMIDE.

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Mutat Res; 85(5):347-356 1981

The effect of various cyclophosphamide (CP) concentrations on sister chromatid exchange (SCE) frequency and cell proliferation, and the influence of experimental parameters (S9 concentration, concentration of cofactors, and exposure time) on CP-induced effects were examined in a human WBC test. The S9 fraction was prepared from livers of Aroclor-induced male rats. S9 mix alone did not influence SCE frequency or cell proliferation. CP, 1.7 x 10(-6) to 5.0 x 10(-5) M, produced increasing delay in cell proliferation. CP-induced SCE frequencies were strongly dependent on actual S9 concentration; cell proliferation was delayed with increasing S9 concentration. Studies with different concentrations of the cofactors (NADP and glucose-6-phosphatase in a ratio of 1:2) indicated an influence on the activity of S9 mix which was not as important as S9 concentration: SCE frequency increased, but cell proliferation was slightly inhibited with prolonged exposure times. CP at 1.7 x 10(-5) M was toxic in exposures greater than 2 hr. The importance of varying experimental parameters to avoid false-negative results in microsome tests is discussed. (28 Refs)

57. METAL MUTAGENS AND CARCINOGENS EFFECTIVELY DISPLACE ACRIDINE ORANGE FROM DNA AS MEASURED BY FLUORESCENCE POLARIZATION.

Richardson CL, Verna J, Schulman GE, Shipp K, Grant AD
Meloy Laboratories, Inc., 6715 Electronic Drive, Springfield, VA, 22151
Environ Mutagen; 3(5):545-553 1981

Investigations were conducted to determine if DNA interactions with nonintercalative agents could be measured in the acridine orange displacement assay, to study the relative DNA reactivity of carcinogenic and noncarcinogenic metals in this system, and to determine if a correlation between DNA binding and mutagenic or carcinogenic effects could be established. Initial studies with cis-dichlorodiammineplatinum (II) (cis-Pt) demonstrated that acridine orange displacement from DNA, as measured by fluorescence polarization, was a direct result of cis-Pt-DNA binding. When the assay was applied to 13 additional metals, a concentration-dependent inhibition of acridine orange-DNA binding was noted. The shapes of the dose-response curves were generally sigmoidal. The interactions of the 13 metals with DNA were observed within 2 min and remained constant over 2 hr, in contrast with cis-Pt interaction which was optimal at 20 hr. Sodium, potassium, and lithium salts required the highest concentration for activity to displace acridine orange, the activities for the carcinogenic/mutagenic metals were substantially lower, and the activities of magnesium and calcium were intermediate. Thus, this assay provides a relative measure of the interaction of metals with DNA, and this DNA reactivity shows a positive correlation with the mutagenic/carcinogenic potential. (35 Refs)

58. USE OF EXONUCLEASE III TO DETERMINE THE SITE OF STABLE LESIONS IN DEFINED SEQUENCES OF DNA: THE CYCLOBUTANE PYRIMIDINE DIMER AND CIS AND TRANS DICHLORODIAMMINE PLATINUM II EXAMPLES.

Royer-Pokora B, Gordon LK, Haseltine WA

Dept. Pathology, Sidney Farber Cancer Inst., Harvard Medical Sch., 44 Binney St., Boston, MA, 02115

Nucleic Acids Res; 9(18):4595-4609 1981

A method to detect chemically stable lesions in DNA has been developed using Exonuclease III, a double strand specific nuclease, to digest 5'-end labeled DNA. The products, when analyzed on high resolution DNA sequencing gels, reveal the sites of DNA modification. Cyclobutane pyrimidine dimers induced by UV irradiation can be localized by comparison of the fragments produced by Exonuclease III digestion with fragments obtained after digestion of the DNA with UV specific endonuclease. The experiments demonstrate that Exonuclease III stops one base away from the cyclobutane pyrimidine dimers. Similar experiments with cis- and trans-dichlorodiammine-platinum (II) showed that modifications of DNA by these agents also impede Exonuclease III digestion. In general the same stop sites were found for cis- and trans-platinum adducts. They occur at sites of adjacent guanine bases. Additional stop sites were found for cis-platinum at sites of adjacent guanine bases. These results are in agreement with the model that cis-platinum forms intrastrand guanine-guanine dimers, whereas trans-platinum does not. (Author abstract) (31 Refs)

59. THE MUTAGENIC EFFECT OF CIS-DIAMMINEDICHLOROPLATINUM II AND ITS DEGRADATION PRODUCTS IN THE AMES MICROBIAL ASSAY.

Peer RL, Litz DA

(c/o Litz) Toxicology Dept., Bristol Laboratories, Syracuse, NY, 13201

Environ Mutagen; 3(5):555-563 1981

The Ames microbial mutagenicity assay was used to test the mutagenicity of cis-diamminedichloroplatinum (II) (cis-DDP) and its degradation products (obtained from a soln aged for 12 mo at 37 C), platin B salt, magnus red, and magnus red anion salt in order to determine if the positive mutagenic response of the platinum compound could be due to, or enhanced by, the presence of degradation products. A significant increase in hist+-revertants occurred with Salmonella strains TA98, TA100, TA92, and TA94 with platin B salt, magnus red, magnus red anion salt, and lyophilized cis-DDP. The aged cisplatin, however, exhibited an increase only with strains TA100, TA92, and TA94. All degradation products exhibited a slight but significant mutagenic effect with strains TA1535 and TA1537. The mixed function oxidase activation system was required for mutagenicity only in the positive control ethidium bromide. These results indicate that platinum degradation complexes are weak mutagens which can induce both base pair and frameshift-type mutations. (32 Refs)

60. CHEMICAL SYNTHESIS OF RADIOLABELED BLEOMYCIN A2 AND ITS BINDING TO DNA.

Roy SN, Orr GA, Brewer FC, Horwitz SB
Dept. Molecular Pharmacology, Albert Einstein Coll. Medicine, Bronx, NY, 10461
Cancer Res; 41(11,part1):4471-4477 1981

A method for the preparation of biologically active [3H]- and [13C]bleomycin A2 is described. Demethyl Cu(II):bleomycin A2, isolated after pyrolysis of Cu(II):bleomycin A2, was methylated with either [3H]- or [13C]methyl iodide, which resulted in Cu(II):bleomycin A2 labeled in the dimethylsulfonium moiety. Copper was removed by treatment with dithizone in chloroform, and structures were verified by thin-layer chromatography and 1H and 13C magnetic resonance spectroscopy. Copper-free [3H]- and [13C]bleomycin A2 are active in the degradation of DNA in vitro. Gel exclusion chromatography and equilibrium dialysis were used to determine the apparent equilibrium constants for binding of [3H]bleomycin A2 and Cu(II):[3H]bleomycin A2 to calf thymus DNA, noncovalently associated polydeoxyguanylate:polydeoxythymidylate, and noncovalently associated polydeoxyadenylate:polydeoxythymidylate. In 2.5 mM sodium phosphate buffer, pH 7.0, binding data obtained by gel filtration with calf thymus DNA reveal an apparent equilibrium constant for [3H]bleomycin A2 of 5.7 x 10(5)/mol and for Cu(II):[3H]bleomycin A2 of 3.9 x 10(5)/mol. One molecule of [3H]bleomycin A2 binds for every 3.7 base pairs in DNA, and one molecule of Cu(II):[3H]bleomycin A2 binds for every 2.8 base pairs in DNA. Analysis of binding data with calf thymus DNA, noncovalently associated polydeoxyguanylate:polydeoxycytidylate, and noncovalently associated polydeoxyadenylate:polydeoxythymidylate obtained by equilibrium dialysis reveals, in each instance, two types of binding sites for both the copper and metal-free form of the antibiotic. For those sites in calf thymus DNA with tighter binding affinity, the apparent equilibrium constant for [3H]bleomycin A2 was 6.8 x 10(5)/mol and for the Cu(II):[3H]bleomycin A2 complex, 4.4 x 10(5)/mol. As seen with calf thymus DNA, the affinity of [3H]bleomycin A2 is slightly greater than that of Cu(II):[3H]bleomycin A2 for the synthetic DNAs, although more of the copper form of the drug binds to these polymers. (Author abstract) (35 Refs)

61. INDUCTION OF GLUCOCORTICOID-RESISTANT VARIANTS IN A MURINE THYMOMA LINE BY ANTITUMOR DRUGS.

Huet-Minkowski M, Gasson JC, Bourgeois S
(c/o Bourgeois) Regulatory Biology Lab., Salk Inst., San Diego, CA, 92183
Cancer Res; 41(11,part1):4540-4546 1981

Several antitumor drugs are shown to be mutagenic in murine thymoma lines: mitomycin C, bleomycin, streptonigrin, Colcemid, and BD40, an analog of ellipticine. Using conditions yielding 3 to 40% cell survival, all five drugs tested increase the frequency of glucocorticoid-resistant variants. Mitomycin C is as efficient as the classical alkylating agents N-methyl-N'-nitro-N-nitrosoguanidine and ethyl methanesulfonate. The other drugs, previously untested for mutagenic activity on mammalian cells, are weak mutagens yielding variants at frequencies one to two orders of magnitude lower than the alkylating agents. All 152 variants obtained result from defects in the glucocorticoid receptor. Variants induced by mitomycin C, streptonigrin, Colcemid, and BD40 have very reduced receptor activity, as measured by dexamethasone binding. In contrast, bleomycin or the combination of mitomycin C and dexamethasone induce a majority of variants having dexamethasone-binding activity comparable to the parental line. However, assays of nuclear transfer capacity and genetic complementation show that these receptors are nonfunctional and may result from point mutations in the gene encoding the glucocorticoid receptor. This study suggests that, in combination therapies, antitumor drugs might induce glucocorticoid-resistant lymphoid cell variants that could be selected by the hormone. (Author abstract) (27 Refs)

62. EFFECT OF THE TUMOR PROMOTER PHENOBARBITAL ON MEMBRANE-MEDIATED PROPERTIES OF ADULT RAT LIVER-DERIVED EPITHELIAL CELLS IN CULTURE (MEETING ABSTRACT).

Shimada T, Kreiser DM, Williams GM
Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
In Vitro; 17(3):224 1981

We have reported a promoting action of phenobarbital on the transformation of adult rat liver (ARL) epithelial cells in culture. We report here various other biological effects of phenobarbital (PB) which mimic induction of transformation on ARL cells. A clonal line of ARL cells, which was proved to be nontumorigenic when examined for transformation markers, was seeded at a density of 1.2 x 10(4) cells/cm2 in Williams Medium E supplemented with heat-inactivated fetal bovine serum at 10% (WME:HIFBS(10)) with gentamicin at 50 ug/ml. Cells were fed with WME:HIFBS10 containing 10(-4) M PB 2 x a wk starting 24 hr after seeding and subcultured once a wk at the same seeding density. Cells that received multiple treatments of PB showed a 10-20% increase in cell population at each subculture up to 10 treatments, and continued to increase in 2-Deoxy-D-glucose (2DG) uptake in the absence of PB by as much as 77% after 22 treatments. On the other hand, single PB treatment of ARL cells did not enhance 2DG uptake. Neither single nor multiple treatments with PB induced anchorage independency in ARL cells. It is suggested that the alteration of plasma membrane properties by PB, as in vivo could be the mechanism of the tumor promoting activity of PB. (2 Refs)

63. ENHANCING EFFECT OF BARBITAL ON N-2-FLUORENYLACETAMIDE-INDUCED RAT LIVER LESIONS.

Mori H, Tanaka T, Nishikawa A, Takahashi M, Williams GM
Dept. Pathology, Gifu Univ. Sch. of Medicine, 40 Tsukasa-machi, Gifu 500, Japan
Gan; 72(5):798-801 1981

The enhancing effects of phenobarbital (PB) and barbital on hepatotumorigenesis were compared by quantitative analysis of the behavior of altered foci following discontinuation of N-2-fluorenylacetamide (FAA) administration. Thirty-four male ACI rats, 2 mo old, were fed 0.02% FAA diet for 13 wk and some of them were sacrificed immediately. The remaining rats were divided into three groups and given a basal diet (Group I) or 0.05% PB diet (Group II) or 0.05% barbital diet (Group III) and sacrificed sequentially at 8 and 16 wk after the beginning of administration of each diet. The number of altered foci detected in hematoxylin and eosin stained or iron stained specimens per cm2 of the liver space at 16 wk in Group I was much lower than that at termination of FAA feeding. However, the numbers of Groups II and III were well maintained at 8 and 16 wk and those at 16 wk in both groups were significantly higher than that in Group I (p less than 0.001). These data show that barbital could be an enhancer of hepatotumorigenesis like PB. (Author abstract) (25 Refs)

64. TUMOR PROMOTION AND PROSTAGLANDINS (MEETING ABSTRACT).

van Rooijen LA, Bisschop A
Department of Carcinogenesis and Mutagenesis, National Institute of Public Health, Bilthoven, The Netherlands
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

The tumor promotors 12-O-tetradecanoylphorbol-13-acetate (TPA) and phenobarbital both appear us to induce the activity of rat hepatic ornithine decarboxylase (ODC). This induction is dose de pendent, with an optimum dose at 20 ug -0.1 mg TPA per kg body wt and at 100 mg phenobarbital per kg body wt. The ODC activity has a maximal value at 4 hr after ip injection of the tumor promotor. It further is protein- and RNA-synthesis dependent. Treatment with retinyl-acetate one hr prior to TPA results in a dose dependent inhibition, being 85% at 20 mg per kg body wt, of the induce ODC activity. Retinyl-acetate at this dose fails to inhibit the phenobarbital induced activity. Analogical pretreatment with indomethacin shows an inhibition of the induced ODC activity, which raises the suggestion of the involvement of prostaglandins in the sequence of events from the application of the tumor promotor to the increase in activity of rat hepatic ornithine decarboxylase. Ip application of prostaglandins (PG E2 and PG F2alpha) both appear to inhibit ODC activity. These two observations possibly suggest a difference in mode of action between intra- and extracellular prostaglandins. (no Refs)

65. EFFECT OF HALOTHANE ANESTHESIA ON PHYTOHEMAGGLUTININ-INDUCED LYMPHOCYTE BLAST TRANSFORMATION.

Gadalov VP, Kuz'mina EG
Res. Inst. Medical Radiology, Obninsk, USSR
Vestn Akad Med Nauk SSSR; (8):53-57 1981

The effect of halothane anesthesia on phytohemagglutinin induced lymphocyte blast transformation (LBT) was studied in 31 patients with lung diseases (29 men, 2 women; 26-70 yr old) undergoing diagnostic bronchoscopy. Of 31 patients, 15 had nonspecific inflammatory lesions and 16 had lung cancer. The index of LBT in cancer patients did not differ from that in the patients with nonspecific lung diseases. Significant inhibition of LBT was recorded after anesthesia in an optimal regimen. (27 Refs) (In RUS)

66. AN ULTRASTRUCTURAL STUDY OF MOUSE LUNG TREATED WITH ISONIAZID (INH) AND ITS ANTI-TOXICANTS.

Kandarkar SV, Maru GB, Bhide SV, Sirsat SM
Cancer Res. Inst., Tata Memorial Centre, Parel, Bombay 400 012, India
Indian J Cancer; 18(3):194-197 1981

The pathogenic morphological changes in lung tissue induced by the tuberculostatic drug isonicotinic acid hydrazide (INH) and the protective effects of its antitoxicants were studied in three- and six-wk old male Swiss mice. Animals were injected ip with 0.09 mg INH/g body wt. Some mice were injected ip with L-arginine, L-sodium glutamate, pyridoxine, or folic acid The dose for the amino acids was 0.9 mg/g body wt. The dose for vitamins was 0.45 mg/g body wt. All animals were sacrificed after 24 hr and lung tissue was examined. Normal Type II lung cells were characterized by membrane-bound cytosomes, mitochondria, a few endoplasmic reticulum profiles, small vesicles, one or more Golgi complexes, and multivesicular bodies. Tissues from antitoxicant-treated controls appeared normal. Type II cells from animals treated with INH were enlarged and contained hypertrophied nuclei. Increased chromatin was densely marginated in some cells. Mitochondria were swollen. Ribosomes, multivesicular bodies, and small vesicular bodies were increased. Cytosomes were enlarged and either contained lamellar material or were empty. Type II cells from mice treated with INH plus antitoxicant appeared normal. This suggest that antitoxicants protect vulnerable lung tissue from the effects of INH. (14 Refs)

67. PROSTAGLANDIN SYNTHETASE MEDIATED ACTIVATION OF P-DIMETHYLAMINOAZOBENZENE (BUTTER YELLOW) (MEETING ABSTRACT).

Vasdev S, Tsuruta Y, O'Brien P
Department of Biochemistry, Memorial University of Newfoundland, Newfoundland, Canada
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

The oral administration of dimethylaminoazobenzene (DAB) induces rodent liver tumors, mouse lung tumors and dog bladder tumors. It is believed that the activation by the liver of DAB involves liver microsomal mixed function catalyzed sequential N demethylation and N hydroxylation reactions. A cytosolic sulfotransferase then catalyzed the conjugation of the N-OH derivative with sulfate to form an electrophilic species which can bind to nucleic acids and protein. This electrophile is considered to be the ultimate carcinogenic metabolite. An alternative metabolic activation should now be considered. It has been found that prostaglandin synthetase can catalyze the binding of C14 DAB to microsomal protein. Extensive N demethylation occurred and C14 4-methylaminoazobenzene was much more effective at binding to the protein than DAB. Arachidonate was also more effective than NADPH with mouse lung and dog bladder microsomes. Cumene hydroperoxide was also much more effective than NADPH with rat liver microsomes. However, cytochrome P 450 was the catalyst for the latter hydroperoxide reaction as in this case extensive 4' hydroxylation also occurred. (no Refs)

68. SPECIES DIFFERENCES IN MUTAGENICITY, COVALENT PROTEIN BINDING AND NEPHROTOXICITY OF THE FLAME RETARDANT TRIS(2,3-DIBROMOPROPYL) PHOSPHATE (MEETING ABSTRACT).

Soderlund E, Dybing E, Nelson SD
Department of Toxicology, National Institute of Public Health, Olso, Norway
Acta Pharmacol Toxicol; 49(Suppl1):48 1981

Tris(2,3-dibromopropyl)phosphate (Tris-BP), the major flame retardant formerly used in US sleepwear, is a potent mutagen, a nephrocarcinogen and an acute nephrotoxin. Hepatic microsomes from rats, mice, hamsters, and guinea pigs are all able to activate Tris-BP to mutagenic products in the Salmonella microsome quantitative reversion assay, mice microsomes being the most and guinea pig microsomes the least active. Phenobarbital (PB)-pretreatment increases the mutagenic activity with all microsomal preparations, whereas 3-methylcholanthrene (MC)-pretreatment decreases Tris-BP mutagenicity in rats and mice and gives a moderate increase in hamsters and guinea pigs. Hepatic microsomes from all species tested have approx similar basal capabilities in converting Tris-BP to covalently protein bound products in vitro; PB-pretreatment increases binding rates in all preparations. MC-pretreatment increases Tris-BP covalent binding with hamster and guinea pig microsomes but not with microsomes from rat or mouse liver. Tris-BP binds covalently to liver protein in vivo in all species and to kidney protein in hamster, guinea pig and mouse to the same degree. In rat kidneys, on the other hand, seven fold higher protein binding levels are found compared to liver, correlating with the finding that kidney is the target organ in this species. None of the other species showed any Tris-BP-induced kidney damage. (no Refs)

69. ANALYSIS OF MUTAGENIC ACTIVITY OF NITROFURYLACRYLIC ACID.

Zhurkov VS, Shram RIa
A. N. Sysin Inst. General and Commune Hygiene, Moscow, USSR
Vopr Pitan; (4):63-67 1981

The potential mutagenic activity of sodium salt of 3-(5-nitro-2-furyl)acrylic acid (5-NFA) currently used as a wine stabilizer was tested in random-bred ICR-SPF mice. Single or repeated 5-NFA administration (intragastrically or with drinking water) did not induce the dominant lethals, chromosome aberrations, or point mutations. (13 Refs) (In RUS)

70. EXPOSURE TO CARCINOGENIC CHEMICALS AND SMOKING INCREASES URINARY EXCRETION OF MUTAGENS IN HUMANS.

Dolara P, Mazzoli S, Rosi D, Buiatti E, Baccetti S, Turchi A, Vannucci V
Istituto di Farmacologia e Tossicologia, Viale Morgagni 65, Florence, Italy
J Toxicol Environ Health; 8(1/2):95-103 1981

The Salmonella/microsome test was employed to test for mutagenic chemicals in 24-hr urine samples in male unexposed controls and workers in two chemical plants. Workers in one plant were exposed to solvents and dyes, in the other to pharmaceutical compounds; operations were carried out in open manner. Both groups ranged in age from 25-50 yr, mean for controls was 36, for workers 41. A baseline for mutagenic activity was determined by dose response curves obtained by plating variable vol of the urine of smoking controls. With tester strain TA1538, urine of nonsmoking chemical workers showed higher mutagenic activity than that of controls with in vivo metabolic activation. Urine of smoking controls and smoking workers showed no difference. There was a difference between smoking and nonsmoking controls. With tester strain TA100 the urine of both smoking and nonsmoking workers showed greater mutagenic activity than controls. When the urines of 10 nonsmoking workers with positive mutagenic activity were tested 20 days after a leave, mutagenicity in some individual was reduced. Although the practice of smoking produced some diff iculties, the results indicate the usefulness of the Salmonella/microsome mutagenicity test in human urine. (9 Refs)

71. METRONIDAZOLE. A REVIEW OF ITS POSSIBLE CARCINOGENICITY AND MUTAGENICITY.

Bostofte E, Bak JF, Hoier R
Gynaekologisk obstetrisk afdeling, Kobenhavns amts sugehus i Herlev, Copenhagen, Denmark
Ugeskr Laeger; 143(35):2211-2214 1981

Studies on the possible teratogenic and mutagenic effects of metronidazole are reviewed. The study of a group of 771 women who had been treated with metronidazole at least once (750 mg/day for 7-10 days) for vaginal trichomoniasis during the period 1960-1969 revealed 40 cases of cancer, including 16 cases of carcinoma in situ of the uterine cervix, which were excluded. The incidence, determined on the basis of the 24 remaining cases, was slightly but insignificantly higher than expected. Only the number of lung cancer was increased significantly (four cases instead of 0.6), but it was believed to be due to smoking rather than to metronidazole treatment. In another group of patients treated with metronidazole for vaginal trichomoniasis during the period 1969-1973, 45 cases of cancer were found against the expected number of 33.3. This was explained by the increased number of cancer of the uterine cervix, while the incidence of the other forms of cancer was not increased. A similar high frequency of cancer of the uterine cervix was found among patients with untreated trichomoniasis. A cytogenic effect was found in cultures of human lymphocytes after long-term treatment with metronidazole, but not after conventional treatment. Carcinogenic effects were found in some experiments in mice and rats, and mutagenic effect presumably caused by a reduced derivative of metronidazole, was demonstrated in various bacterial systems. It is concluded that the mutagenic and carcinogenic effects of metronidazole are not yet fully elucidated, but in normal doses (600-1,000 mg/day for 7-10 days) the risk is apparently negligible. (30 Refs) (In DAN)

REVIEWS AND OTHER COMPOUNDS

72. CHROMOSOME ABERRATIONS AND THEIR RELEVANCE TO METAL CARCINOGENESIS.

Vainio H, Sorsa M
Dept. Industrial Hygiene and Toxicology, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Environ Health Perspect; 40:173-180 1981

Current knowledge of the effects of metals on chromosomes is reviewed, and gaps in this knowledge and future research needs are discussed. The subjects covered include detection of somatic chromosome damage by analysis of metaphase chromosome aberrations (CAs), scoring for sister chromatid exchange, and scoring for micronuclei in maturing RBC; genetic effects of somatic CAs; chromosome changes in malignancies; correlations between CAs and immunologic impairment and aging; CAs in humans exposed to metal compounds (arsenic, cadmium, chromium, nickel, mercury, and lead): and the health implications of chromosome damage caused by metal exposure. A group of exposed persons with increased CA levels has a higher risk of developing cancer than a group with no increase in CAs. However, the quantitative risk estimate cannot be deduced from chromosome data for a single individual; on an individual basis, increased chromosome damage may also point to inherited susceptibility. (73 Refs)

73. EFFECT OF METALS ON MUTAGENESIS AND DNA REPAIR.

Rossman TG
Inst. Environmental Medicine, New York Univ. Sch. Medicine, 550 First Ave., New York, NY, 10016
Environ Health Perspect; 40:189-195 1981

A review is presented of mechanisms of mutagenesis, effects on DNA repair leading to comutagenesis, and possible reasons why carcinogenic metals are not mutagenic in microbial systems. A classification of mutagenesis mechanisms is based on the possible modes of action of metals: misreplication due to altered DNA or decreased fidelity of DNA polymerase, inhibition of proofreading, and mutagenesis via error-prone DNA repair. Excision repair, mismatch repair, and two other alternative pathways (not involving cleavage of the phosphodiester bond and subsequent repair replication characteristic of excision repair) are discussed with respect to effects on DNA repair leading to comutagenesis. Bacteria have an inducible, error-prone DNA repair system (SOS repair) whose activity results in mutagenesis. In one of the best studied examples of metal mutagenesis, chromate, little evidence exists for involvement of the SOS system. Arsenite exemplifies metals that may act as comutagens by inhibiting repair of damage to DNA caused by another agent. Comutagens would not be detected by standard screening methods. (48 Refs)

74. CHELATING AGENTS IN BIOLOGICAL SYSTEMS.

Schubert J
Dept. Chemistry, Univ. Maryland Baltimore County, Catonsville, MD, 21228
Environ Health Perspect; 40:227-232 1981

A review is presented of selected aspects of the chemistry of metal ions, chelate formation, and stability of metal chelates. Subjects discussed include chelate formation and in vivo stability (including rate effects), mixed (ternary) complexes, oxidation-reduction, and biological consequences and applications (including lipophilicity and intracellular transport, catalase-like activity, and viral interactions). Complexes and chelates of platinum(II) such as cis-dichlorodiammineplatinum are useful in cancer chemotherapy. Other active Pt complexes include those in which one ligand is bidentate, such as dichloroethylenediammineplatinum. These Pt compounds could conceivably interact with DNA via ternary complex formation. The ability to use mixed complex formation as a ligand scavenger for transporting ligands makes possible utilization of nontoxic binary chelates for the transport of chemotherapeutic drugs to target sites. Metal and ligand scavenging play a role in the induction or reversal of mutagenic effects. The so-called role of metals in carcinogenesis could reflect transport of binary and ternary complexes of the metals to and from intracellular target sites. (32 Refs)

75. SECOND ANNUAL REPORT ON NATIONAL CANCER INSTITUTE AND ENVIRONMENTAL PROTECTION AGENCY PROJECTS.

Department of Health and Human Services
Public Health Service, NIH, Bethesda, MD
Second Annual Report on National Cancer Institute and Environmental Protection Agency Projects. Bethesda, MD, National Cancer Institute, 384 pp., 1981.

Current projects underway under the auspices of the National Cancer Institute and the Environmental Protection Agency are described. Progress reports are presented for the following: a data base for chemicals identified in human biological media; in vivo analysis of UV-B-induced photooxidations; use of the hairless mice for carcinogenesis studies; chronic toxicity and carcinogenicity to rats and mice of chloroform in drinking water; the effects of carcinogens, mutagens, and teratogens on non-human (aquatic) species; the cost effectiveness of two types of personal UV-B dosimeters; the effects of varying doses of UV on mammalian skin; immunodiagnostic markers for breast cancer; antigens on human lymphoid organs for the immunodiagnosis of leukemias and lymphomas; human epithelial cell metabolic activation systems for use with human cell mutagenesis; evaluation of the transformation assay using C3H 10T1/2 cells for use in screening chemicals for carcinogenic potential; national mortality data bases for environmental epidemiology; epidemiologic field studies on ecological relationships between specified toxic substances and cancer morbidity and mortality; an epidemiologic study of populations in Turkey previously exposed to hexachlorobenzene; a case control study of lung, pancreas, and stomach cancer in Southern Louisiana; support services for epidemiologic studies of lung cancer in communities with non-ferrous smelters; an epidemiologic study of the incidence of cancer as related to industrial emissions in the heavily industrialized parts of Contra Costa County in California; an environmental data base for New Jersey to be used in epidemiological studies; an etiologic study of respiratory cancer in coastal Texas; and completion of the NCI/NCHS cooperative study of 1972 mortality data. (no Refs)

76. CANCER PREVENTION - PRINCIPLES AND PROBLEMS.

Schramm T
Zentralinstitut fur Krebsforschung, Akademie der Wissenschaften der DDR, Lindenberger Weg 80, 1115 Berlin-Buch, E. Germany
Z Aerztl Fortbild (Jena); 75(11/12):526-529 1981

The general principles, approaches and problems in primary cancer prevention are discussed. The majority of all cancers in humans are caused directly or indirectly by exogenous factors. The major causes of cancer include tobacco, alcohol, sunlight, industrial chemicals, radiation, drugs, and possible factors determined by the life style. The existence of threshold doses for carcinogenic factors has not yet been clarified. The individual cancer risk is determined by the interplay of such processes as carcinogenesis, cocarcinogenesis, syncarcinogenesis, and anticarcinogenesis. The possibility of nitrosation of 61 drugs available in East Germany was investigated: slight nitrosation of ethambutol, piperazine, aminophenazone Analgin, desipramine, imipramine, clomipramine, ampicillin, oxacillin, and phenoxymethylpenicillin was determined. It was possible to inhibit but completely suppress the nitrosation of these drugs by the addition of ascorbic acid. (22 Refs) (In GER)

77. HUMAN SALIVA INACTIVATES MUTAGENICITY OF CARCINOGENS.

Nishioka H, Nishi K, Kyokane K
Div. Biochemistry, Doshisha Univ., Kyoto, Japan
Mutat Res; 85(5):323-333 1981

Various carcinogens, suspected carcinogens, certain pyrolysates (beef, salmon, sodium glutamate, polypeptone), and cigarette smoke condensate (CSC) were incubated with human saliva from healthy subjects. Effects on mutagenicity were tested in a modified Ames test with Salmonella typhimurium strains TA 98 and TA 100. Metabolic activation for development of mutagenicity was required by aflatoxin B1, benzo(a)pyrene (BP), tryptophan pyrolysate-1 (Tr-P-1, isolated from boiled beef), the other pyrolysates, and CSC. No metabolic activation was required by 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2; a nitrofuran used as a food additive during 1966-1975 in Japan), N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), methyl methanesulfonate (MMS), 4-nitroquinoline 1-oxide (4NQO) and quercetin. Saliva inactivated AF-2, MNNG, 4NQO, aflatoxin B1, BP, and Trp-P-1. Mutagenic activities of quercetin, pyrolysates of beef, salmon, and sodium glutamate, and CSC decreased to some extent; the activities of MMS and polypeptone pyrolysate were not affected. Boiled saliva inactivated AF-2 somewhat in TA 98 but not in TA 100 cultures. Complex mechanisms may be involved in the inactivation of mutagenicity of carcinogens by saliva. (22 Refs)

78. DOES EVERYTHING CAUSE CANCER?

Jacobson M
Center for Science in the Public Interest, 1755 S St., N.W., Washington, DC, 20009
Med Self Care; 14(2):38-40 1981

The growing number of substances labeled 'cancer-causing' has caused fear and confusion. The most important factors individuals can control are cigarette smoking, high fat/high cholesterol diet, polluted workplaces, alcohol abuse, salt, sedentary lifestyle, and unnecessary drugs. Avoidance of carcinogens should be based on a calculation of risk. (no Refs)

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CHEMICAL CARCINOGENESIS

1. CHEMICAL COMPOUNDS AND CANCER RISK.
Schramm T, Jansch W
Zentralinstitut fur Krebsforschung der Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin, E. Germany
Arch Geschwulstforsch; 51(7):561-565 1981
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Pershagen G
Dept. Environmental Hygeine, Karolinska Inst., Stockholm, Sweden
Environ Health Perspect; 40:93-100 1981

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Norseth T
Inst. Occupational Health, Gydas vei 8, Oslo 3, Norway
Environ Health Perspect; 40:121-130 1981

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Kazantzis G
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Sunderman FW
Dept. Lab. Medicine, Univ. Connecticut Sch. Medicine, Farmington, CT, 06032
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Piscator M
Dept. Environmental Hygiene, Karolinska Inst., S-104 01 Stockholm, Sweden
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Schubert J
Dept. Chemistry, Univ. Maryland Baltimore County, Catonsville, MD, 21228
Environ Health Perspect; 40:227-232 1981

8. BENZENE AS A RISK FACTOR.
Stobbe H
Universitatsklinik fur Innere Medizin 'Theodor Brugsch', Bereich Medizin der Humboldt-Universitat, Schumannstrasse 20/21, DDR-1040 Berlin, E. Germany
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800-A Fifth Ave., Suite 503, New York, NY, 10021
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Hardell L, Eriksson M
Onkologiska kliniken, Regionsjukhuset, Umea, Sweden
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DIETARY FACTORS IN CARCINOGENESIS

13. NUTRITIONAL MODULATION OF CANCER.
Nauss KM, Newberne PM
Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139
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Harington JS
Cancer Res. Dept., Natl. Cancer Assoc. South Africa, P.O. Box 2000, Johannesburg 2000, South Africa
JNCI; 67(5):977-989 1981

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Int J Epidemiol; 10(2):127-133 1981

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Clemmesen J
(c/o P. Lohman), Medical Biological Lab. TNO., P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(1):65-79 1981

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19. THE ROLE OF METALS IN CARCINOGENESIS: BIOCHEMISTRY AND METABOLISM.
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Dept. Chemistry, Dartmouth Coll., Hanover, NH, 03755
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Becker FF
M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Am J Pathol; 105(1):3-9 1981

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Harvey RG
Ben May Lab., Univ. Chicago, Chicago, IL, 60637
Acc Chem Res; 14(7):218-226 1981

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Squibb KS, Fowler BA
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
Environ Health Perspect; 40:181-188 1981

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Grossman L
Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 N. Wolfe St., Baltimore, MD, 21205
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Zakour RA, Kunkel TA, Loeb LA
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Environ Health Perspect; 40:197-205 1981

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Vainio H, Sorsa M
Dept. Industrial Hygiene and Toxicology, Inst. Occupational Health, Haartmaninka tu 1, SF-00290 Helsinki 29, Finland
Environ Health Perspect; 40:173-180 1981

MODIFICATION OF CARCINOGENESIS

26. METAL INTERACTIONS IN CARCINOGENESIS: ENHANCEMENT, INHIBITION.
Nordberg GF, Andersen O
Dept. Environmental Hygiene, Umea Univ., Umea, Sweden
Environ Health Perspect; 40:65-81 1981

27. EFFECT OF METALS ON MUTAGENESIS AND DNA REPAIR.
Rossman TG
Inst. Environmental Medicine, New York Univ. Sch. Medicine, 550 First Ave., New York, NY, 10016
Environ Health Perspect; 40:189-195 1981

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Latt SA, Allen J, Bloom SE, Carrano A, Falke E, Kram D, Schneider E, Schreck R, Tice R, Whitfield B, Wolff S
Harvard Medical Sch., Boston, MA, 02115
Mutat Res; 87(1):17-62 1981

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Sirover MA
Dept. Pharmacology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Environ Health Perspect; 40:163-172 1981

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HYDRAZINES AND RELATED COMPOUNDS

1. EFFECT OF INHIBITORS OF TUMORIGENESIS ON THE FORMATION OF O6-METHYLGUANINE IN THE COLON OF 1,2-DIMETHYLHYDRAZINE-TREATED RATS.

Bull AW, Burd AD, Nigro ND
Wayne State Univ. Sch. Medicine, Detroit, MI, 48201
Cancer Res; 41(12):4938-4941 1981

The level of O6-methylguanine (O6MeGua) in the colonic DNA of rats treated with 1,2-dimethylhydrazine was determined. The effect of various tumorigenesis inhibitors on the formation of this modified base was also studied. Rats were

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given a single sc injection of 1,2-[14C]dimethylhydrazine. Six hours later, they were killed, and colonic DNA was extracted and analyzed by high-pressure liquid chromatography. The inhibitors tested were disulfiram (DSF), pyrazole, sodium selenite, butylated hydroxyanisole, butylated hydroxytoluene, potassium ascorbate, and 13-cis-retinoic acid. The level of O6MeGua in control rats was 29.9 [(O6MeGua x 10(6)/guanine)]. When rats were fed 0.25% (w/w) DSF, this value was reduced to 10.2, and at 0.5% DSF there was not detectable O6MeGua formed. Injection of pyrazole (40 mg/kg ip) 2 hr prior to 1,2-dimethylhydrazine treatment reduced the O6MeGua level to 2.4. All the other tumorigenesis inhibitors had no effect on either O6MeGua levels or the cpm/mg DNA in treated rats. With O6MeGua as a measure of the extent of initiation, these results confirm that DSF and pyrazole inhibit the initiation phase of carcinogenesis. This is to be expected as both have been shown to block the metabolism of azoxymethane, which is a crucial metabolite in the activation of 1,2-dimethylhydrazine. The other substances, all known tumorigenesis inhibitors, may act on the promotional phase of carcinogenesis and are worthy of further study for their role in cancer prevention. (Author abstract) (22 Refs)

2. THE RESPONSE OF THREE INBRED STRAINS OF RAT TO THE CARCINOGEN 1,2-DIMETHYLHYDRAZINE.

Teague CA, Gavin JB, Herdson PB
(c/o Gavin) Dept. Pathology, Univ. Auckland, Private Bag, Auckland, New Zealand
Pathology; 13(3):473-485 1981

Rats of three inbred strains (DA, HS and AS2) were dosed with 1,2-dimethylhydrazine 2HCl (DMH) or saline by gavage weekly for 10 wk. DA and HS rats showed little overt toxic reaction but all AS2 rats died following DMH doses of 30 mg/kg. However, at 10 mg/kg 60% of AS2 rats survived the 30 wk experiment. All DA rats developed a high yield of adenocarcinoma of the bowel (means: males 6.8 tumors/large bowel and 0.8/small bowel; females 2.8/large and 0.08/small bowel) and one-third of the males developed tumors of the ear canal. A smaller proportion (52%) of HS rats developed tumors, specifically bowel tumors (means: male 1.4/large and 0.2/small bowel; females 0.4/large and 0.1/small bowel). Even on the lower dose of DMH AS2 rats showed extensive liver changes including cystic cholangioma (58%), angiosarcoma (25%) and hepatocellular carcinoma (8%) and 83% developed bowel tumors (means: males 2.3/large and 1.5/small bowel; females 3.5/large and 1.0/small bowel). The rapid induction and high yield of bowel tumors, the different toxicity of DMH in AS2 rats, and the differences in relative tumor density both between sexes and in the various segments of the bowel indicate the potential of these strains for studies of carcinogenesis in the bowel. (Author abstract) (32 Refs)

3. DETECTION OF HYALURONECTIN OR MESENCHYME ASSOCIATED ANTIGEN IN THE EARLY STAGES OF COLONIC CARCINOGENESIS INDUCED BY 1-2 DIMETHYLHYDRAZINE (MEETING ABSTRACT).

Halkin E, Delpech B, Laumonier R, Tayot J, Delapierre F
Centre Henri Becquerel, Rue d'Amiens, 76 038 Rouen Cedex, France
Oncodev Biol Med; Abstracts Book,1:P17 1981

This study dealt with the detection of a protein 'hyaluronectin' in the colon of 1,2-Dimethylhydrazine treated rats. Hyaluronectin is a hyaluronic binding glycoprotein that is associated with fetal, reactive or cancerous mesenchyme. Immunohistochemistry study used the indirect method with an immune-serum conjugated with peroxidase. The dose dependence, the latency period of hyaluronectin production in tumors and preneoplastic lesions have been studied. It is concluded that hyaluronectin could be considered as a marker of the changes in colon tissue from the time of initiation in carcinogenesis. (no Refs)

4. QUANTITATION OF A MUTAGENIC METABOLITE PRODUCED FROM 1,2-DIMETHYLHYDRAZINE DURING LIPID INFLUENCED COLON CANCER DEVELOPMENT BY A BACILLUS SUBTILIS ASSAY.

Wargovich MJ
Texas Tech University, Lubbock, TX, 79409
Diss Abstr Int [B]; 42(4):1330-B 1981

The positive correlation between intake dietary fat and cancer of the colon is well documented. Studies were conducted using an experimental colon carcinogenesis model to determine the role of dietary fat in the metabolism of the colon carcinogen, 1,2-Dimethylhydrazine (DMH). Bacillus subtilis TKJ6321 was used to quantify fecal mutagen and postmitochondrial enzyme in the liver and the colon mucosa of rats fed diets variable in lipid content and treated ip with DMH. Corn oil or coconut oil were used as the source of lipid for the diets. During a 32 wk schedule rats were sacrificed and autopsied for evidence of adenocarcinoma of the colon. Fecal samples were extracted and assayed for mutagenic activity by B subtilis TKJ6321 as the microbial detector of mutagenicity. Rats fed corn oil in the diet and treated with DMH produced a significantly higher number of adenocarcinomas of the colon. When the lipid content of the diet was raised to 10% (wt/wt) corn oil markedly stimulated enzyme induction in animals receiving DMH treatment. This induction was especially pronounced in the mutagen-producing enzyme activity of the colonic mucosa. Treatment of rats with DMH induces enzyme in the liver and colon relevant for the conversion of this compound to a mutagenic species. The extent of enzyme activity is influenced by the type of lipid supplementing the diet as is subsequent colon tumor development. (no Refs)

5. A STUDY OF THE ONCOGENIC CAPACITY OF INHALED MONOMETHYLHYDRAZINE (MEETING ABSTRACT).

Kinkead ER, Haun CC, Vernot EH, MacEwen JD
Toxic Hazards Research Unit, P.O. Box 3067, Dayton, OH
Toxicologist; 1(1):132 1981

Rats, mice, hamsters and dogs were exposed to monomethylhydrazine (MMH) by the inhalation route for one yr using an industrial work wk schedule of 6 hr/day, 5 days/wk with holidays and weekends off to simulate a human occupational exposure regimen. All rodents were held for an additional yr of observation at which time necropsies were performed on survivors and approx 33 tissues were taken for histopathologic evaluation of tumorigenesis following the NCI protocol. The dogs will continue to be held for additional postexposure observation. Concentrations tested were 0.02, 0.2, 2.0 and 5.0 ppm as well as unexposed controls. A dose-response relationship in body wt gain and mortality was noted in several species. The growth of the exposed beagle dogs two yr postexposure is comparable to their respective controls and blood parameters have remained within normal ranges. (no Refs)

6. THE ONCOGENIC HAZARD FROM CHRONIC INHALATION OF HYDRAZINE.

Carter VL, Back KC, MacEwen JD

Toxic Hazards Div., Aerospace Medical Res. Lab., Wright-Patterson Air Force Base, OH

Sci Tech Aerosp Rep; 19(18):2532-2533 1981

Studies were therefore conducted to evaluate the long term effects of airborne hydrazine at levels near the present and proposed threshold limit value concentrations. Repeated daily inhalation exposure to 5 parts per million (ppm) hydrazine induced nasal tumors in Fischer 344 male and female rats and in male Golden Syrian hamsters. Repeated exposure to 1 ppm also produced nasal turbinate tumors in rats and pulmonary adenomas in female C57B1/6 mice. The inhalation exposures to the rodents were conducted for 6 hr per day, 5 days per wk over a 12 mo period. Rats and mice were held 18 mo postexposure. The nasal turbinate tumor incidence in rats was dose related. No statistically significant tumorigenic effects occurred after repeated exposure to 0.05 and 0.25 ppm hydrazine concentrations which spanned the American Conference of Governmental Industrial Hygienists recommended threshold limit value. (Author abstract) (no Refs)

7. TOXICITY AND MUTAGENICITY OF HYDRAZINE AND THREE METHYLATED DERIVATIVES IN L5178Y MOUSE LYMPHOMA CELLS (MEETING ABSTRACT).

Rogers AM, Back KC

Air Force Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, OH

Toxicologist; 1(1):40 1981

Heritable effects can be detected in mammalian cells in culture using changes in gene functions as an end-point. The function of different genes can be revealed by the use of selective agents. The four selective systems used here are ouabain, thymidine, thioguanine and cytosine arabinoside. Previous work with a series of compounds in L5178Y mouse lymphoma cells has indicated that they may possess mutagen specific activity. Hydrazine, monomethylhydrazine (MMH), 1,1-dimethylhydrazine (UDMH) and 1,2-dimethylhydrazine (SDMH) have been examined for toxicity and mutagenic potential. The compounds exhibit marked differences in toxicity. MMH is the most toxic compound followed by hydrazine, UDMH and SDMH. This correlates well with the toxicity of these compounds in vivo as the same relative toxicities were observed in the mouse. Hydrazine, UDMH and SDMH induced mutation in the thymidine selective system in the absence of extraneous metabolic activation. Dose-response curves were produced for these compounds. MMH did not induce thymidine mutation in the presence or absence of extraneous metabolic activation. All four compounds were negative in the ouabain, thioguanine and cytosine arabinoside selective system. Induction of mutation by hydrazine and UDMH is correlated with toxicity. This is not the case for SDMH-induced mutation. Hydrazine, UDMH and SDMH appear to have different modes of action in the cell. (no Refs)

HETEROCYCLIC COMPOUNDS

8. ENHANCED SUSCEPTIBILITY TO AFLATOXIN B1 TOXICITY IN WEANLING MICE PRETREATED WITH CARBON TETRACHLORIDE.

Arora RG

Dept. Pathology, Coll. Veterinary Medicine, K. C. S-750 07 Uppsala, Sweden

Acta Pathol Microbiol Scand [A]; 89(4):303-308 1981

Weanling male mice with or without prior treatment with CCl4 (0.5 ml/kg) were exposed to either single (20.5, 25.6, 32 and 40 mg/kg) or multiple (4 mg/kg for 10 days or 8 mg/kg for 5 days) doses of aflatoxin B1. Evidence o its acute toxic and carcinogenic effects was found only in CCl4 pre-treated mice. Single dose LD 50 value under these conditions was calculated to be 26.8 mg/kg. Histological changes which predominantly occurred in the liver were characterized by acute necrosis and degeneration of the parenchymal cells. Hepatomas were observed as early as 9 mo of age in CCl4 pre-treated animals given 4 mg/kg aflatoxin daily for 10 days. It is thus suggested that the repeated use of CCl4 as an anthelmintic in animals which are apparently resistant to the lethal and hepatocarcinogenic action of aflatoxin might increase their sensitivity to this mycotoxin. (Author abstract) (20 Refs)

9. MUTAGENESIS OF INTACT PARVOVIRUS H-1 IS EXPRESSED CO-ORDINATELY WITH ENHANCED REACTIVATION OF ULTRAVIOLET IRRADIATED VIRUS IN HUMAN AND RAT CELLS TREATED WITH 2-NITRONAPHTHOFURANS.

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Carcinogenesis; 2(10):1039-1043 1981

The possibility of a relationship between enhanced mutagenesis (EM) and enhanced reactivity (ER) of intact virus in 2-nitronaphthofuran-treated human and rat cells was tested. 2-Nitro-7-methoxy-naphtho[2.1-b]furan (R7000) and 2-nitro-7-bromo-naphtho[2.1-b]furan (R7160) were compared for their ability to trigger the generation of mutations in progeny of intact parvovirus H-1 and repair of UV-irradiated H-1. Both R7000 and R7160 triggered the coordinate expression of two cellular activities: mutator activity, which caused mutations among descendants of intact virus, and repair activity, which reactivated UV-damaged virus. R7000, which was more active in the Salmonella typhimurium reversion assay than R7160, also was a more potent inducer of both mutator and repair activities. ER and EM had similar amplitudes and displayed parallel time courses and dose responses. Activation of both functions was delayed after cell treatment and was transient; it showed bell-shaped dependency on the naphthofuran concentration and required de novo protein synthesis. The results showed that chemicals can enhance mutagenesis of undamaged DNA by activating expression of mutator functions in mammalian, including human, cells. (20 Refs)

10. INHIBITION OF DNA SYNTHESIS IN RELATION TO ENHANCED SURVIVAL OF UV-DAMAGED HERPES VIRUS IN MONKEY CELLS TREATED BY A VARIETY OF 2-NITRONAPHTHOFURANS.

Nocentini S, Coppey J, Buisson JP, Royer R
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Mutat Res; 90(2):125-135 1981

The effects of various 2-nitronaphthofuran (2NNF) derivatives on immediate inhibition of normal DNA synthesis and on the capacity of pretreated CV-1 monkey kidney cell cultures to support replication of UV-damaged Herpes simplex virus (HSV) were investigated. The capacity of treated cultures (40 hr) to support the production of intact virus was inhibited by approx 20% at concentrations eliciting max enhancement of UV-HSV production and by approx 60% at concentrations 3.3x higher. In contrast, after 40 hr of contact with the various compounds, the production of UV-damaged HSV was enhanced. After treatment of cultures with drug concentrations giving greatest reactivation in terms of virus yield, the proportion of cells infected by UV-damaged HSV giving rise to infectious centers was increased. The inhibition of DNA synthesis induced by four representative 2NNF compounds was found to be irreversible at least during the first 4-5 hr of post-treatment incubation; inhibition increases with time. The most efficient 2NNF derivatives, especially 2-nitro-7-methoxynaphtho[2,1-b]furan-R7000, were at least as potent as aflatoxin B1 in inducing virus reactivation. The results indicate that 2NNFs are DNA-damaging agents like chemical carcinogens. (21 Refs)

11. TRANSPLANTATION AND CELL CULTURE OF RAT URINARY BLADDER CARCINOMA.

Cohen SM, Yang JP, Jacobs JB, Arai M, Fukushima S, Friedell GH
Dept. Pathology, St. Vincent Hosp., Worcester, MA, 01604
Invest Urol; 19(3):136-141 1981

Six bladder carcinoma cell lines were established in culture from male Fischer rats fed N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide. Five were papillary transitional cell carcinomas by back transplantation and one was squamous. Each has been maintained in culture for more than 4 yr. The light, transmission, and scanning electron microscopic features of the cells in culture and transplantation are described. (Author abstract) (15 Refs)

12. EFFECT OF REGENERATIVE HYPERPLASIA ON THE URINARY BLADDER: CARCINOGENICITY OF SODIUM SACCHARIN AND N-[4-(5-NITRO-2-FURYL)-2-THIAZOLYL]FORMAMIDE.

Cohen SM, Murasaki G, Fukushima S, Greenfield RE
Dept. Pathology, Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, NE, 68105
Cancer Res; 42(1):65-71 1982

The effect of ulceration of the urinary bladder or bladder carcinogenesis induced by N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) or sodium saccharin was evaluated in 5-wk-old F344 rats which were all killed 2 yr after the start of the experiment. The results indicate that long-term feeding of sodium saccharin, a nonmutagen, appears to be capable of inducing bladder tumors if administered to a rat with a proliferating bladder mucosa even without FANFT 'initiation.' Ulceration was induced by freezing. FANFT was fed at a level of 0.2% of the diet for 2 wk, and sodium saccharin was fed as 5% of the diet for 102 or 104 wk. Ulceration followed immediately by FANFT administration and then by control diet for 102 wk did not result in bladder tumors, whereas FANFT administration followed by ulceration and then control diet for a similar period induced bladder tumors. Ulceration followed by FANFT administration and then by 102 wk of sodium saccharin feeding induced bladder tumors, but ulceration followed by 2 wk of control diet followed by 102 wk of sodium saccharin feeding induced a similar incidence of tumors. Ulceration followed immediately by sodium saccharin (fed for 104 wk) induced a slightly lower incidence of tumors. FANFT followed by sodium saccharin without ulceration induced a single bladder carcinoma, but either chemical alone did not induce bladder tumors. Ulceration of the urinary bladder produced by a single ip injection of cyclophosphamide (100 mg/kg) gave similar results as ulceration by freezing. Ulceration alone induced by freezing or cyclophosphamide was followed by a reversible, regenerative nodular and papillary hyperplasia, and the bladder mucosa returned to normal in 3 to 4 wk after ulceration and remained normal through 2 yr. The lack of enhancing effect of FANFT, a potent mutagen, compared to control diet and ulceration induced by cyclophosphamide, a mutagenic alkylating agent, compared to ulceration induced by freezing support the hypothesis of carcinogenesis occurring without mutation. These results may also help to explain the carcinogenicity of sodium saccharin in two-generation and pellet implantation experiments and may assist in the identification of populations with increased susceptibility to bladder cancer. (Author abstract) (53 Refs)

13. PROSTAGLANDIN HYDROPEROXIDASE-MEDIATED 2-AMINO-4-(5-NITRO-2-FURYL)[14C]THIAZOLE METABOLISM AND NUCLEIC ACID BINDING.

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Cancer Res; 41(12):4961-4966 1981

Prostaglandin hydroperoxide-mediated metabolism and binding of 2-amino-4-(5-nitro-2-furyl)[14C]thiazole ([14C]ANFT) metabolite to nucleic acids and proteins were investigated with rabbit bladder transitional epithelial and solubilized ram seminal vesicle microsomes. Metabolism was assessed by spectrophotometric and radiochemical techniques. Substrate and inhibitor studies are consistent with both metabolism and binding of [14C]ANFT occurring by the prostaglandin hydroperoxidase activity of prostaglandin endoperoxide synthetase. The ratio of the rates of [14C]ANFT product formation is approx 3:7:10 (organic soluble:non-trichloroacetic acid precipitable: trichloroacetic acid precipitable) over a wide range of arachidonic acid concentrations. Approx 2 and 1% of the total [14C]ANFT metabolized binds to transfer RNA and DNA, respectively. The metabolite isolated from the organic phase had a chromatographic profile and UV spectra different from authentic ANFT. If transfer RNA or DNA is added at the end of a 5-min incubation, no binding to nucleic acids was observed. The demonstration of prostaglandin hydroperoxidase-mediated covalent binding to nucleic acids is consistent with the involvement of this enzyme in 5-nitrofuran-induced bladder carcinogenesis. (Author abstract) (44 Refs)

14. IMIDAZOLE DERIVATIVES AS INHIBITORS OF CYTOCHROME P-450-DEPENDENT OXIDATION AND ACTIVATORS OF EPOXIDE HYDROLASE IN HEPATIC MICROSOMES FROM A MARINE FISH.

Little PJ, James MO, Bend JR, Ryan AJ
(c/o James) Dept. Medicinal Chemistry, Coll. Pharmacy, Univ. Florida, Box J4, JHMHC, Gainesville, FL, 32610
Biochem Pharmacol; 30(20):2876-2880 1981

Binding of 4(5)-phenylimidazole, benzimidazole, and naptho(2,3,4',5')-imidazole to cytochrome P-450 in sheepshead hepatic microsomes was examined; effects of these compounds on benzo[a]pyrene metabolism in control and induced microsomes are described. (39 Refs)

15. FLAVONOIDS, MUTAGENS, AND CITRUS.

Horowitz RM
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ACS Symp Ser; 170:43-59 1981

Data on the mutagenicity of flavonoids are reviewed. Of all classes of flavonoids, mutagenicity has been demonstrated only for some of the flavonols. Quercetin had the highest mutagenic activity in the Ames test in Salmonella typhimurium. The validity of the Ames test, however, depends on the activating agents used. Flavonols occur in almost all higher plant tissues and are common in human diets . The most common flavonols are quercetin and kaempferol, which almost always occur in the form of glycosides, which are nonmutagenic. Metabolism of quercetin glycosides is probably carried out along several pathways by intestinal microflora. Any occurrence of mutagenic quercetin aglycone is probably fleeting at most. Animal feeding studies of quercetin carcinogenicity have produced contradictory results. No evidence of absorption of free quercetin by the human gut has been found. Citrus fruits contain a wide variety of flavonoids. Any mutagenic activity of flavonols is probably affected by the presence of other flavonoids. Flavonoids apparently present minimal risk in human diets. (46 Refs)

16. NEOPLASTIC TRANSFORMATION OF HUMAN EPITHELIAL CELLS IN VITRO AFTER EXPOSURE TO CHEMICAL CARCINOGENS.

Milo GE, Noyes I, Donahoe J, Weisbrode S
Comprehensive Cancer Center, Ohio State Univ., 410 West 12th Ave., Columbus, OH, 43210
Cancer Res; 41(12):5096-5102 1981

Human foreskin epithelial cells were transformed to an anchorage-independent state of growth (in soft agar) and neoplasia (invasion of chick embryonic skin in vitro). Aflatoxin B1, N-methyl-N'-nitro-N-nitrosoguanidine, propanesultone, beta-propiolactone, or UV absorbance at 254 nm were used successfully as carcinogens. These foreskin epithelial cells, like human foreskin fibroblasts, were readily transformed when treated in S phase but, unlike the transformed fibroblasts, expression of cellular neoplasia did not require an extended period of time in culture. The invasive features of the transformed human epithelial cells in chick embryonic skin in vitro simulated squamous cell carcinoma. (Author abstract) (29 Refs)

17. INFLUENCE OF MICROINJECTED ALKYLATING AGENTS ON THE DEVELOPMENT OF AMPHIBIAN EGGS.

Ellinger MS, Garone LM
Dept. Zoology, Southern Illinois Univ., Carbondale, IL, 62901
Teratogenesis Carcinog Mutagen; 1(4):389-398 1981

The effects of microinjection of beta-propriolactone (BPL) on developing frog eggs were investigated. Complete failure to cleave and dispersion of egg pigment within 2 hr resulted when 17 nanomoles of BPL were injected. For eggs microinjected with 10 nanomoles of BPL, the greatest postcleavage mortality occurred earlier than for controls. With BPL, 12% of the microinjected embryos arrested during the gastrula to neurula interval. The major defect was a failure to incorporate yolky endoderm cells. Nineteen of 178 eggs injected with 10 nanomoles BPL survived to stage 20. Five of these were abnormal. In one tadpole that had arrested at stage 19, epithelial proliferation and a small neoplasm were found in the left body wall. Cells involved appeared to be derived from the lateral plate mesoderm. Egg microinjection is probably not suitable as a convenient mutagenesis bioassay. (39 Refs)

18. EFFECT OF BETA-GLUCURONIDASE INHIBITOR ON AZOXYMETHANE-INDUCED COLONIC CARCINOGENESIS IN RATS.

Takada H, Hirooka T, Hiramatsu Y, Yamamoto M
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Cancer Res; 42(1):331-334 1982

In this study of the role of microfloral beta-glucuronidase in colonic carcinogenesis, the effect of beta-glucuronidase inhibitor was evaluated. Starting at 5 wk of age, male Donryu rats were fed either a semisynthetic diet or the same diet containing 0.1% beta-glucuronidase inhibitor as N-cyclohexyl-5-O-acetyl-2,4-O-(p-methoxybenzylidene)-D glucaro-1-amide-6,3-lactone (C-GAL). All animals were given sc injections of 7.4 mg azoxymethane (AOM) per kg body wt once a wk for 11 wk and followed for an additional 20 wk. Most animals receiving the colonic carcinogen developed tumors in the colon, and a few also developed tumors in the small intestine. However, the number of tumors in the large intestine of the rats given C-GAL at the same time as AOM was significantly lower than in the control rats, especially in the proximal half of the colon, but those given C-GAL after AOM treatment had almost the same number of colon tumors as did the controls. It is concluded that, since bacterial beta-glucuronidase activity in the feces of rats given 0.1% C-GAL was significantly inhibited, intestinal microfloral beta-glucuronidase may play an important role in colonic carcinogenesis caused by AOM. (Author abstract) (48 Refs)

19. COMPARISON BETWEEN A PURIFIED AND STANDARD DIET ON FANFT-INDUCED MURINE BLADDER CANCER.

Soloway MS, Nissenkorn I, McCallum LW
Dept. Urology, Univ. Tennessee Center Health Sciences, Memphis, TN
Urology; 18(5):482-484 1981

We investigated the effect of two diets containing equal amounts of the carcinogen FANFT on the incidence and induction time of murine bladder carcinoma in mice. At each time interval, the tumor incidence in the mice ingesting a purified, high-cal diet, was equal or greater than the tumor incidence in the animals fed standard mouse chow. The mean animal wt of the mice ingesting the purified diet was consistently higher than that of the mice fed the standard diet. The bladder wt (an index of tumor vol) showed no significant difference between the mice receiving the two diets. Since mice eat to fulfill their caloric requirements, the animals ate less of the purified diet and the cost per mouse per yr was lower. (Author abstract) (6 Refs)

20. CARCINOGENICITIES OF QUINOLINE DERIVATIVES IN F344 RATS.

Fukushima S, Ishihara Y, Nishio O, Ogiso T, Shirai T, Ito N
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Cancer Lett; 14(2):115-123 1981

Carcinogenicity of the quinoline derivatives 6-nitroquinoline (6NQ), 8-nitroquin oline (8NQ), 6-methylquinoline (6-MQ), 8-methylquinoline (8MQ), 8-hydroxyquinoline (8HQ), and 5,7-dibromoquinoline (5,7DQ) was assayed in F344 rats. Animals were fed diets containing 0.05% 6NQ, 0.1% 8NQ, 0.05% 6MQ, 0.05%8MQ, 0.1%8HQ, or 0.1% 5,7DQ ad libitum for 104 wk or until moribund. 8NQ induced forestomach tumors in both male and female rats, including squamous cell papillomas in 28/30 males and 36/37 females, and squamous cell carcinomas in 20/30 males and 24/37 females. The other derivatives tested were not carcinogenic in F344 rats. 6NQ induced areas of focal hyperplasia in forestomach tissue. The results indicate a discrepancy between mutagenic potential of these compounds as measured in the Ames Salmonella/microsome assay and their carcinogenicity in vivo. (13 Refs)

21. EFFECT OF CAFFEINE (CF) ON PANCREATIC CARCINOGENESIS OF 4-HYDROXYAMINO-QUINOLINE 1-OXIDE (4-HAQO) IN RATS (MEETING ABSTRACT).

Konishi Y, Denda A, Yokose Y, Takahashi S
Department of Oncological Pathology, Cancer Center, Nara Medical College, Kashihara, Nara 634, Japan
Newsletter Natl Pancreas Cancer Project; VI(2):31 1981

Sixty male Wistar rats weighing 160 g were used. 4-HAQO, at a dose of 7 mg/kg was given by iv injection and CF was given by sc injection for 12 hr intervals. Group (G) 1 received 4-HAQO at 3 days after partial pancreatectomy (PP) G 2 received 6 x injections of 120 mg/kg of CF before 4-HAQO which was given 3 days after PPGs 3, 4, and 5 received 12 x injections of 120, 60, and 30 mg/kg of CF after 4-HAQO which was given 3 days after PP, respectively. All rats were sacrificed at 52 wk, and examined macroscopically and histologically. The numbers of pancreatic tumors counted macroscopically were 14.9 +/-6.6 in G 1, 10.0 +/-5.9 in G 2, 6.0 +/- in 3.2 G 3, 22.7 +/-8.3 in G 4, and 28.1 +/-11.4 in G 5. These results suggest that CF showed biphasic effects, inhibitory and enhancing ones, on the pancreatic carcinogenesis of 4-HAQO in rats. (no Refs)

22. ALKYLATION OF N2 IN DEOXYGUANOSINE BY DEHYDRORETRONECINE, A CARCINOGENIC METABOLITE OF THE PYRROLIZIDINE ALKALOID MONOCROTALINE.

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Cancer Res; 42(1):8-14 1982

Dehydroretronecine, an antimitotic and carcinogenic agent, reacted with the deoxyguanosine at pH 7.4 in vitro to yield in nearly equal quantities two major adducts, which were isolated by thin-layer and high-pressure liquid chromatography. The adducts were stable at pH 8.7 and 30 C for at least 24 hr, showed pKas at acidic and alkaline pHs, reacted with 4-(p-nitrobenzyl)-pyridine, had a nonexchangeable guan-8-yl proton, and contained equimolar quantities of the pyrrole and nucleotide moieties. From the above data and comparison of proton magnetic resonance spectra of dehydroretronecine, deoxyguanosine, and the adducts, both products were identified as derivatives with a bond between C-7 of dehydrosupinidine and N2 of deoxyguanosine. Mass spectral fragmentation patterns and infrared and UV absorbance spectra were also consistent with N2 substitution. Circular dichroism spectra established the identities of each of the adducts as 7-(deoxyguanosin-N2-yl)dehydrosupinidine; they are enantiomeric at C-7. These results demonstrate that the reactive electrophile derived from protonated dehydroretronecine readily alkylates the N2 position of deoxyguanosine at C-7 in an SN1 reaction to yield a racemic mixture of products. (Author abstract) (34 Refs)

23. POTENT ENVIRONMENTAL TUMOR PROMOTERS FOUND IN STREPTOMYCES AND BLUE-GREEN ALGA (MEETING ABSTRACT).

Fujiki H, Sugimura T, Moore RE

National Cancer Center Research Institute, Tokyo 104, Japan

International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

It is well known that tumor promoters induce ornithine decarboxylase (ODC) activity in mouse skin and that this induction can be inhibited by the application of 13-cis-retinoic acid. These two properties of tumor promoters were utilized for screening new tumor promoters in our environment. Two new classes of tumor promoters are presented: 1) Indole alkaloid (teleocidin and lyngbyatoxin); and 2) Polyacetate (aplysiatoxin and debromoaplysiatoxin). Teleocidin from Streptomyces and lyngbyatoxin, from the blue-green alga, Lyngbya majuscula, were able to induce ODC activity in mouse skin and showed various biological activities similar to those of tetradecanoyl phorbol acetate (TPA). Teleocidin and lyngbyatoxin are indole alkaloids. Their tumor promoting activities became apparent in the mouse skin through a two-stage carcinogenicity test. The tumor incidence of the group treated with dimethylbenzanthracene (DMBA) plus teleocidin was 100% at wk 30, which was similar to that of the group given DMBA and TPA. The in vivo carcinogenicity test with lyngbyatoxin is still underway. The tumor incidence of the group treated with DMBA plus lyngbyatoxin is 80% at wk 21. A second new class of tumor promoter is polyacetate. Aplysiatoxin and debromoplysiatoxin were isolated from another variety of blue-green alga. Aplysiatoxin and debromoaplysiatoxin induced ODC to the same degree of potency. However, aplysiatoxin induced various membrane effects, such as adhesion of cells and turnover of phospholipid with a similar concentration of TPA, teleocidin and lyngbyatoxin. On the other hand, debromoaplysiatoxin required an amount almost 100 x greater to achieve the same effects. (no Refs)

24. PYRAN COPOLYMER AND 7,12-DIMETHYLBENZANTHRACENE-INDUCED CARCINOGENESIS IN THE HAMSTER CHEEK POUCH.

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Arch Oral Biol; 26(10):761-767 1981

The anticarcinogenic action of pyran copolymer (PC) on 7,12-dimethylbenzanthracene (DMBA)-induced carcinogenesis in the cheek pouch of male Golden Syrian hamsters was examined. All hamsters treated topically with DMBA exhibited buccal pouch tumors after 11 wk. None of the animals receiving no treatment (Group 1) or mineral oil alone (Groups 2 and 4) developed tumors. Group 3 (saline- and DMBA-treated) and Group 5 (PC- and DMBA-treated) hamsters displayed mean tumor latent periods of 7.900 and 8.074 wk, respectively. Groups 3 and 5 exhibited mean tumor diameters of 2.7 and 3.0 mm, respectively, at 11 wk. Groups 1-4 included 6 hamsters each; Group 5 was composed of 24 hamsters. One hamster each in groups 1, 2, 3, and 5 died prior to the end of the 11-wk period. No significant difference in carcinoma incidence was observed between Groups 3 and 5 after 11.5 wk. Of Group 3 and 5 hamsters, 100% and 96%, respectively, developed carcinomas. No consistent difference in histologic appearance of carcinomas was observed between Groups 3 and 5. Mean hemagglutinin titers were higher in groups receiving PC than in the saline-treated control groups, but the difference was not significant. Analysis of immunologic findings for Groups 3 and 5 demonstrated a statistically significant difference in respective mean titers ($p = 0.01$). Organ and blood-cell changes were noted only in PC-treated animals. The results indicated that PC had little if any effect on DMBA-mediated buccal pouch carcinogenesis. (27 Refs)

INORGANIC AGENTS AND PARTICULATES INCLUDING FIBERS

25. TISSUE DAMAGE AND NUTRITIONAL FACTORS IN EXPERIMENTAL RESPIRATORY TRACT (CO-) CARCINOGENESIS (MEETING ABSTRACT).

Kroes R, Reuzel PG, Feron VJ, Spit BJ, Beems RB

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International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Co-factors involved in respiratory tract carcinogenesis are studied in Syrian golden hamsters using benzo(a)pyrene as the carcinogenic agent. These factors include severe tissue damage induced by electro-coagulation, glass fibers administered by intratracheal instillation, acetaldehyde as irritant vapor, food restriction, and nutrients such as vitamin A and saturated and unsaturated fats. A combined exposure to four different major gaseous cigarette smoke components viz methyl nitrite and isoprene and one solid cigarette smoke component, nor-harman are examined in short- and long-term inhalation studies. An interesting finding was the carcinogenicity of acetaldehyde, of which the possible mechanism is briefly discussed. Another conspicuous observation was the substantial increase in number and size of lipid droplets in alveolar macrophages of hamsters fed a high vitamin A diet. (no Refs)

26. COCARCINOGENICITY OF FOUNDRY PARTICULATES (MEETING ABSTRACT).

Niemeier RW, Stettler LE, Mulligan LT, Rowland J

No affiliation given

Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

The traditional use of silica sand for metalcasting is slowly being replaced by non-silica aggregates due to increased demands for improved cast surfaces and closer dimensional tolerances, and due to the physical, chemical and biological limitations of silica sands. The major non-silica aggregates presently used throughout the metalcasting world include zircon sand, olivine sand, chromite sand and aluminum silicates. However, little is known about the biological effects of these materials. The sands are currently being evaluated for both fibrogenic and cocarcinogenic potential in the hamster model by intratracheal administration of the commercial sand with or without concurrent administration of benzo(a)pyrene (BaP). Respirable fractions of the sands were prepared either by sieving and/or air classification or by micronizing. Particle size analyses of the respirable fractions showed that more than 99% of each sample was less than 10 um and that surface areas varied from 1.01 to 2.41 m(2)/g. Free silica contents of the nonsiliceous sands were all found to be less than 1%. Chrysotile asbestos were found in both olivine samples and chromite sand. Amphibole fibers were also found in the latter. The study is designed so that the final sacrifice will occur 90 wk from the start of exposure. Interim results are reported here and show that lung tumors have been found in all groups receiving the aggregate plus B(a)P, but no lung tumor bearing animals have been found in the aggregate only groups. The relative severity of the fibrogenic and carcinogenic responses must await final histopathological examination and statistical analyses. (no Refs)

27. SELECTIVE EFFECTS OF METAL IONS ON RNA SYNTHESIS RATES.

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Toxicology; 22(1):9-21 1981

Fourteen chloride metal ions were tested in vitro to determine their effects upon Escherichia coli RNA polymerse transcription of calf thymus and T4 phage DNA. Conditions were altered from previously published reports to insure that metal ions were kept in soln (pH 7.4, omissions of 2-mercaptoethanol). Neither overall synthesis nor chain initiation were altered by the new assay conditions. Increasing concentrations of metal ions inhibited transcription in the order Pb2+ greater than Zn2+ greater than Cu2+ greater than Cd2+ greater than Ni2+ greater than Ca2+ greater than Co2+ greater than Mn2+. Be2+ had a stronger inhibitory effect than Cd2+ at low concentrations but less so at higher concentrations. Sr2+ had very little effect. At concentrations of Ca2+, Mg2+, Sr2+, Zn2+, Li+, Na+, and K+, that decreased overall transcription chain initiation was also decreased. These metals are considered to be non-mutagenic and non-carcinogenic. Co2+, Mn2+, and Cd2+, metals that are mutagenic and carcinogenic, caused marked stimulation in chain initiation at concentrations that inhibited overall transcription. BeCl2 and PbCl2, both known carcinogens, caused only a wide range of concentrations that inhibited overall transcription. (42 Refs)

28. TOXICITY, MUTAGENESIS AND CO-MUTAGENESIS OF CADMIUM (CD) IN SALMONELLA MUTANTS TA98 AND TA100 (MEETING ABSTRACT).

Rubin RJ, Kroll R

Department of Environmental Health Sciences, Johns Hopkins University, Baltimore, MD, 21205

Toxicologist; 1(1):25 1981

The role of cadmium as a carcinogen has been controversial. In the widely used bacterial assay of Ames for mutagens/carcinogens the metals have routinely been reported to be negative. In the present study the mutagenesis and co-mutagenesis of Cd along with its toxicity was studied in TA98 and TA100. Cd, at the concentrations indicated, was added to the media used to prepare the solid agar plates onto which the test bacteria were poured. Exposure to Cd occurred during the 48 hr incubations on the solid agar. Toxicity tests were carried out on nutrient agar while mutagenesis and co-mutagenesis were performed on histidine-deficient agar. TA98 was inhibited 50% by 2.5 x 10(-6) M Cd but was unaffected by 2.5 x 10(-8) M and lower; TA100 was less sensitive and was inhibited 50% by 1.25 x 10(-4) M and was unaffected by 2.5 x 10(-5) M and lower. Zn, at non-toxic levels, completely protected against the toxicity of Cd at Zn: Cd M ratios of 4:1 for TA98 and 1:1 for TA100. At nontoxic levels Cd had no mutagenic effect on TA98 but increased the mutagenicity of a known direct-acting mutagen, hycanthone (Hyc) 3-4 fold. The same degree of enhancement of Hyc mutagenicity by non-toxic levels of Cd was seen in TA100. Lucanthone (Luc), an indirect-acting mutagen, has been shown to give rise to Hyc following S9 activation. No effect of Cd was seen on the mutagenicity of Luc in a S9 supplemented system, suggesting inhibition of activation, thereby offsetting Cd enhancement of any Hyc that would be formed. No effect of Cd was seen on another direct-acting mutagen, methylnitro-nitrosoguanidine. These data indicate that Cd may act as a co-mutagen for certain mutagenic agents and suggest a possible co-carcinogenic role for this metal. (no Refs)

29. MUTAGENICITY OF A SERIES OF HEXACOORDINATE CHROMIUM(III) COMPOUNDS.

Warren G, Schultz P, Bencroft D, Bennett K, Abbott EH, Rogers S

Dept. Chemistry, Montana State Univ., Bozeman, MT, 59717

Mutat Res; 90(2):111-118 1981

A series of 17 substitutionally inert chromium(III) compounds were synthesized and their genetic toxicity investigated in a differential DNA repair assay (DR) or the Salmonella histidine reversion assay (Ames assay). Genetic toxicity in both systems was critically dependent upon the ligand composition of the chromium(III) complexes. Compounds tested showed a parallel between mutagenicity in the Ames test in Salmonella and differential inhibition in the DR test in Escherichia coli. The greater the differential inhibition in the repair test, the more likely it was that a compound would be mutagenic in the Salmonella system. Four of the 17 compounds tested were positive in both systems, while 4 compounds were less active in the repair assay and negative in the Ames test. The remaining nine were negative in both assays. Three of the four most active complexes had four stable aromatic amine ligands, a charge of plus one, and two more labile ligands in a cis-configuration. Chromium(III) in the proper ligand environment can have considerable genetic toxicity and could represent one of the several possible ultimate species in a mechanism for chromium mutagenesis and carcinogenesis. (36 Refs)

30. BINDING PATTERNS OF CARCINOGENIC AND NON-CARCINOGENIC NICKEL PARTICLES TO VARIOUS CELLULOSE PAPERS (MEETING ABSTRACT).

Abbracchio MP, Bonura J, Caprioli RM, Costa M

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Toxicologist; 1(1):155 1981

Crystalline Ni3S2 and NiS induce neoplastic transformation in cultured Syrian hamster embryo cells while amorphous NiS lacks carcinogenic activity. All three compounds were of similar particle size (3-4 um) and were essentially insoluble in aqueous systems. Amorphous NiS was also 3 x less toxic to cell colony survival than crystalline NiS and Ni3S2 particles but amorphous NiS particles were not phagocytized. Comparison of binding properties of these metal compounds to soluble cellular fractions such as RNA, DNA and protein showed no differences and presented numerous technical problems in assaying particulate metal binding. We then studied the binding of these compounds to cellulose (C), diethylaminoethyl-C (DEAE), phospho-C (P-C) papers offering differently charged surfaces. Circular paper discs (6mm) suspended on curved needles attached to the cover of Petri dishes were immersed in a mixture of metal particles (50ug/ml) suspended in 10mM phosphate buffer pH 7.0. The discs were washed with metal-free buffer and the concentration of bound nickel particles determined in each disc by means of x-ray fluorescence spectrometry. The following levels (ppm) of nickel were present in each disc for crystalline NiS: DEAE-C equals 16, C equals 9, P-C equals 36; for amorphous NiS: DEAE-C equals 1, C equals 0.4, P-C equals 87. When DEAE-C discs were impregnated with apparently saturating amounts of crude cell homogenates, crystalline NiS bound more than amorphous NiS. The differences in biological effects between crystalline NiS and amorphous NiS particles may be further elucidated using this binding technique to examine charge affinities between metal particles and cellular material. (1 Ref)

31. COMBINED ACTION OF CHROMIUM AND NICKEL ON MOUSE AND HAMSTER FIBROBLAST CELL LINES.

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J Hyg Epidemiol Microbiol Immunol; 25(3):252-258 1981

Cytotoxic effects of trivalent Cr(III) and hexavalent Cr(VI) chromium and bivalent nickel Ni(II) and of their combinations were tested on suspension cultures of mouse fibroblast line L-A 115. Cytogenetic analysis was performed on the Chinese hamster cell strain 237-2a. Hexavalent chromium (10(-3)-10(-5) M) was lethal for mouse fibroblasts. Concentrations 10(-6) M and 10(-7) M produced considerable cell growth inhibition. Trivalent chromium ions (10(-3)-10(-6) M) had no influence on cell growth. Bivalent nickel ion (10(-3) M) was lethal; 10(-4) M concentrations inhibited cell growth by approx 25%. The combination of two non-toxic concentrations, 10(-5) M Ni(II) and 10(-3) M Cr(III), produced approx 50% growth inhibition. Cytogenetic analysis of Chinese hamster cells revealed a linear correlation between the number of detected aberrant cells and the applied concentration of bivalent nickel and trivalent chromium ions [Ni(II) 10(-5)-10(-7) M; Cr(III) 10(-3)-10(-5) M]. After exposure to the combination Ni(II) 10(-5) M x Cr(III) 10(-3) M which was inhibitory to cellular growth, only simple summation of actions occurred. A similar result was obtained after exposure to the combination at a lower concentration Ni(II) 10(-7) M x Cr(III) 10(-5) M. In contrast, after the Ni(II) 10(-6) M x Cr(III) 10(-4) M combination the number of induced aberrations was significantly ($p = 0.01$) lower than that anticipated after summation of actions; the phenomenon may result from stimulation of cellular repair mechanisms. (10 Refs)

32. EFFECTS OF CADMIUM IN VITRO ON BENZO(A)PYRENE METABOLISM BY RAT TESTICULAR AND HEPATIC MICROSOMES (MEETING ABSTRACT).

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Toxicologist; 1(1):121 1981

Cadmium is known to have toxic effects on the testes as well as to inhibit microsomal mixed function oxidase activity in a variety of tissues. Studies were carried out to compare the actions of cadmium in vitro on testicular and hepatic metabolism of benzo(a)pyrene (BP), a compound which requires metabolic activation for its mutagenic and carcinogenic effects. Testicular and hepatic microsomes were obtained from normal male rats and incubated with BP in the presence of saturating concentrations of NADPH and varying (2 x 10(-4) M -5 x 10(-6) M) concentrations of cadmium. In liver microsomes, cadmium produced a dose-dependent decrease in the production of fluorescent metabolites (phenols). By contrast, in testicular microsomes, the lower concentrations of cadmium (2.5 and 5 x 10(-5) M) enhanced the formation of phenols whereas higher levels (greater than 1 x 10(-4) M) decreased the production of fluorescent metabolites. To determine if the changes in testicular production of phenolic metabolites might be related to alterations in competing metabolic pathways, the effects of cadmium on the activity of epoxide hydrase, an enzyme required for the production of dihydrodiol metabolites, were investigated. Cadmium produced a dose-dependent inhibition of epoxide hydrase activity in both testicular and hepatic microsomes. The effects in testes were greater than those in liver. Preliminary analysis of BP metabolites by high performance liquid chromatography further indicates that cadmium affects the production of both phenols and dihydrodiols by testicular and hepatic microsomes. The results demonstrate that cadmium alters the routes of metabolism of BP in the testes and may therefore, influence its toxicity. (no Refs)

33. THE EFFECT OF DIETARY SELENIUM ON THE METABOLISM AND EXCRETION OF THE HEPATOCARCINOGEN 2-ACETYLAMINOFLUORENE IN THE RAT.

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Diss Abstr Int [B]; 42(4):1412-B 1981

Hepatic enzymes, presumably involved in the metabolism of the hepatocarcinogen 2-acetylaminofluorene (AAF), were examined in rats fed a Torula yeast-based selenium-deficient diet or the same diet supplemented with 0.5 ppm selenium (as sodium selenite). Selenium-deficient rats exhibited almost total absence of hepatic selenium-dependent glutathione peroxidase activity three wk after initiation of test diet feeding. Dietary selenium had no significant effect on hepatic soluble sulfotransferase activity in vitro as measured with the substrates, N-hydroxy-AAF and phenol. Hepatic lipid peroxidation (HLP) was not altered by AAF-challenge in rats fed either diet. In agreement with previous reports, dietary selenium protected against increased HLP produced by administration of carbon tetrachloride. Selenium-supplemented rats exhibited (a) no significant change in the production of 7-,5-, and N-hydroxy-AAF metabolites and (b) significantly increased production of 3-hydroxy-AAF metabolite as compared to selenium-deficient rats. Dietary selenium had no significant effect on total metabolites excreted or on the major phenolic metabolites excreted into the free-glucosiduronic acid-conjugated, or sulfuric acid-conjugated fractions. However, selenium-deficient rats excreted two and three x more N-hydroxy-AAF into the free-, and glucosiduronic acid-conjugated fractions, respectively. These findings tend to support the hypothesis that dietary selenium alters the in vivo metabolism of AAF in a manner that selectively decreases N-hydroxy-AAF excretion, and possibly its production. Thus dietary selenium's protective effect against AAF-induced hepatocarcinogenesis may be partially explained by the ability of selenium to decrease the amount of N-hydroxy-AAF available for further activation. (no Refs)

34. INVESTIGATION OF THE MUTAGENICITY OF PARTICULATE EXTRACTS OF CITY AIR FROM BERLIN.

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Haustechnik Bauphys Umwelttech; 102(5):263-265 1981

Particulate matter collected from the air over Berlin during a 2-mo period was analyzed for mutagenicity and content of polycyclic aromatic hydrocarbons (PAHs). Extracts of the particulates were mutagenic in Salmonella typhimurium strains TA98 and TA100. The degree of mutagenicity of the particulates collected at different times varied. Analysis of the PAH content of the samples revealed that some contained benz(a)pyrene. (7 Refs) (In GER)

35. STUDIES ON THE MUTAGENIC EFFECTS OF EXTRACTS DERIVED FROM AIRBORNE PARTICULATES WITHIN ONE YEAR IN DIFFERENTLY BURDENED AREAS USING THE AMES TEST.

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Zentralbl Bakteriol [Orig A]; 172(4/5):351-366 1981

Season variations of the mutagenicity of extracts of suspended matter in air samples collected at monthly intervals in 1978 from three sites were assayed by the Ames test. The three sites were Duisburg (DU; mines), Dusseldorf (D; a residential city), and Krahm (K; rural district). Mutagenicity was tested in the presence of both S-9 and NADPH and with each cofactor alone. Results are presented as the number of revertants related to air vol, wt of suspended matter, wt of dried extract and to the amount of benzo(a)pyrene (BP) in the extract. Mutagenicity varied according to the BP concentration in the atmosphere with values highest in winter, lowest in summer. When mutagenicity was based on BP content, it was nearly constant throughout the yr at site DU or rose in summer (sites D and K). These results indicate that the larger part of the pollutants may originate from the same sources as BP (eg incomplete combustion). Direct mutagenicity (assayed without activating system) was somewhat higher in winter than in summer. However, these differences are minimal or lacking when mutagenicity was expressed as number of revertants per wt suspended matter or dried extract. Mutagenicity reached a max in summer, provided the number of revertants was related to BP concentration. The latter results indicate that the direct acting mutagens present in the air originated from other sources than that of BP (eg, automobile exhaust). Mean values of mutagenicity related to number of revertants per dry wt and wt of suspended matter did not differ among the three sites. It can be assumed that composition of particulate matter may be similar with respect to mutagens regardless of the level of pollution. (10 Refs) (In GER)

36. RADIATION CARCINOGENESIS. COMPREHENSIVE FINAL REPORT, 16 MAY 1979-31 DECEMBER 1980.

Warren S, Brown CE, Gates O
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Radiation Carcinogenesis. Comprehensive Final Report, 16 May 1979-31 December 1980. Available from National Technical Information Service, Springfield, VA, as DOE/EV/03017-43:, 29 pp., 1981.

This abstract covers three main areas of investigation: mesothelioma induction by asbestos, radiation tumorigenesis and transplantable tumors. Canadian and Rhodesian asbestos fibers have been administered under anesthesia to rats by intratracheal, intrapleural and ip injection. Additional groups were given 3-methylcholanthrene or x-radiation along with asbestos. A large series of mice also treated as above have displayed mesotheliomas. In addition, glass fiber injections and feeding of asbestos were done and have produced negative results to date. The carcinogenic effect of whole-body radiation on hemi-irradiated parabiont partners exposed to a single 1,000 R dose of x-ray was evidenced by a significant increase in the incidence of malignant tumors in only six tissues: skin, supporting soft tissue, kidney, bone, pancreatic islets and ovary. In the male adrenal medulla and in the female breast genetic and parabiotic hormonal factors were judged to exert a significant effect. The occurrence of incisional (anastomotic) sarcomas in significant numbers in hemi-irradiated and parabiont control pairs suggests the operation of mechanical factors complicating the healing process, only slightly enhanced by radiation. One of the very valuable but unanticipated developments of the rat radiation program was the isolation of two transplantable endocrine tumors with strong hormonal potentials: an insulinoma of the pancreas and a pheochromocytoma of the adrenal medulla. (Author abstract)

37. THE RELATIONSHIP OF AIR POLLUTION TO LUNG CANCER IN CONTRA COSTA COUNTY (MEETING ABSTRACT).

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Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

Contra Costa County, a nearly 2000 km2 area in the northeastern part of the San Francisco Bay Area, has a population of more than 600,000. It was one of 39 counties in the US which has been shown to have high mortality rates for specific cancer sites. The northern section of the county is heavily industrialized with five major petroleum refineries and many chemical plants. This project was designed to examine the relationship between air pollution in Contra Costa County and the incidence of cancer. Contra Costa County cancer incidence data for the period 1969-78 were available through the RCE's population-based registry, now a part of the NCI's SEER Program. Particulate air pollutants were collected and analyzed under an Environmental Protection Agency (EPA) grant. Hi-vol glass filters were collected every sixth day for one yr, from November, 1978, through October, 1979, at each of fifteen sampling stations. Particulate matter was analyzed for total suspended particulates (TSP), benzene-soluble organics (BSO), sulfates (S0(4)), nitrates (N0(3)), lead (Pb), selected polycyclic aromatic hydrocarbons (benzo(a)pyrene, benzo(ghi)perlene, benzo(a)anthracene, chrysene and for some samples, coronene), and mutagenicity using the Ames test. Estimates of the av annual level of each of the measured pollutants are computed for the population centroids of each of the 115 census tracts in the county. The industrialized portion of the county was found to have an age-adjusted incidence rate of lung cancer which has increased over the 10 yr of study from about a 10% excess to about a 60% excess as compared to the non-industrial portion. The correlation of each air pollutant and of several combinations of the pollutants with lung cancer incidence is under examination. In addition, a case-control interview study of lung cancer, using population-based controls, is underway. Major factors under examination are smoking, occupation, diet and alcohol, air pollution and proximity to one of the 18 toxic waste dump sites, found only in the industrial portion of the county. (no Refs)

AMIDES, CARBAMATES AND UREAS

38. SULFATE-DEPENDENT METABOLIC ACTIVATION OF 2-ACETYLAMINOFLUORENE BY PRIMARY CULTURES OF ADULT RAT HEPATOCYTES (MEETING ABSTRACT).

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Toxicologist; 1(1):35 1981

The role of sulfate in the metabolic activation of the model aromatic amine hepatocarcinogen 2-acetylaminofluorene (2AAF) was determined using primary hepatocyte cultures as a cellular model of the liver. Adult male rat hepatocytes were isolated by collagenase perfusion of the liver and maintained in collagen-coated dishes with hormone-supplemented, chemically defined media. Cytochrome P-450 levels were fully maintained in the cultures for 48 hr. After 28 hr, the cultures were incubated with 67-137 ng of [14C]2AAF. Polar metabolites were isolated by chloroform-water partitioning, and bound carcinogen residues were measured as non-extractable radioactivity incorporated into hepatocellular trichloroacetic-acid-insoluble material. In an experiment using sulfate-free medium, sulfate supplementation doubled the level of bound residues at 2 and 3 1/2 hr but had no effect at 21 hr. Culture media containing 0, 0.1, 0.5 and 1.0 mM sulfate respectively produced 0.8, 1.4, 3.6 and 4.8% bound residues in a 3 hr incubation. Sulfate supplementation did not effect the overall rate of 2AAF metabolism. Phenol, at 1 uM in sulfate-free media, doubled the level of bound residues. Galactosamine, at 2mM, reduced by half the level of bound residues in cultures incubated with 2AAF and 1mM sulfate. These findings support the importance of sulfoconjugation in the metabolic activation of 2AAF. (no Refs)

39. THE EFFECT OF CAFFEINE ON TWO-STAGE SKIN CARCINOGENESIS AND ON COMPLETE SYSTEMIC CARCINOGENESIS.

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Carcinogenesis; 2(10):977-979 1981

The effect of a single large dose of caffeine (100 ug/g, sc) on skin and lung tumorigenesis in female ICR mice, using urethan as an initiator and anthranil as a promoter, was investigated. Topical treatment with urethan and anthranil resulted in a 37%

(11/30) incidence of papilloma-bearing mice, with an av of 1.27 papillomas/mouse. Caffeine significantly augmented tumor incidence (to 60%) when injected 6 hr before initiation. Caffeine produced a smaller increase in the incidence of papillomas when administered 9 hr before initiation, whereas it was associated with an insignificant decrease when administered 6 hr after initiation. Induction of lung adenomas by urethan was unaffected by caffeine administration. The results suggest that timing of a large single dose of caffeine might determine the direction of its gene-modulating effect. (16 Refs)

40. LEUKEMOGENIC EFFECT OF URETHANE ADMINISTERED TOGETHER WITH ESTROGENS TO MICE.

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Egeszsegtudomany; 25(3):251-255 1981

Effects of carcinogenic and noncarcinogenic substances administered together with estrogens or urethane were studied in 6-8-wk-old male CFLP mice. Each substance was administered in three individual doses during an 18-day period, and the results were evaluated after 300 days. Lung tumors and lymphomas were found in the animals treated with ethyl formate (500 mg/kg), phenylurethane (100 mg/kg), pyrene (5 mg/kg), and their combinations with diethylstilbestrol (DES: 25 mg/kg), but there was no significant difference in the percentage of tumor-bearing animals between the treated animals and the untreated controls. Other groups were treated with dimethylnitrosamine (10 mg/kg), benzo(a)pyrene (5 mg/kg), or 3-methylcholanthrene (5 mg/kg), or their combinations with DES. There was no significant difference in tumor frequency between the groups treated with the carcinogens only and those treated with the carcinogens and DES. Solid tumors in the abdominal cavity and hepatic tumor were also found in addition to lung tumors and lymphomas in the DES-treated groups. Other groups were treated with urethane with or without BCG or Escherichia coli endotoxin (ET): the carcinogenic effect of urethane was not modified by BCG and ET. In other experiments, urethane induced multiple lung tumors with and without DES, but the number of lymphomas was significantly higher in the group treated with urethane and DES than in the groups treated with urethane or DES alone. (24 Refs) (In HUN)

41. STRUCTURAL IDENTIFICATION OF THE PROTEIN COVALENT ADDUCT FORMED IN VIVO IN RAT LIVER AFTER THIOACETAMIDE TREATMENT (MEETING ABSTRACT).

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Toxicologist; 1(1):1 1981

Thioacetamide is a much studied hepatocarcinogen which previously has been reported to bind covalently to cellular macromolecules in vivo and after metabolism in vitro. This investigation addressed the problem of structural identification of the protein adduct which is formed in vivo in rat liver after thioacetamide administration. The subcellular distribution of radiolabeled thioacetamide indicated that the microsomal fraction had significantly higher levels of covalently bound material than did the nuclear, mitochondrial, or cytosolic fractions which had nearly identical levels when expressed on a per mg protein basis. Pretreatment of the rats with either 3MC or PB did not significantly alter the amount or the subcellular distribution of covalently bound radioactivity from control values. The covalent adducts to amino acids were isolated from cytosolic protein by enzymatic digestion followed by ion exchange chromatography. Seventy percent of the covalently bound material eluted as a single peak between proline and glycine on an amino acid analyzer. Acid hydrolysis of the purified adduct released lysine and radiolabeled acetate quantitatively. The purified adduct and a standard of N-6-acetyl-lysine co-chromatographed on an amino acid analyzer and on gas chromatography. The isolated adduct and the standard had identical mass spectra. Thus the major protein adduct formed by thioacetamide in vivo is N-6-acetyl-lysine. (no Refs)

42. INCREASED ACTIVITY OF A NEUTRAL PROTEASE IN CYTOSOL FROM RAT HEPATOMA INDUCED BY N-2-FLUORENYLACETAMIDE.

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Cancer Res; 41(12):5130-5133 1981

A protease active with N-alpha-benzoyl-DL-arginine-p-nitroanilide with an optimum pH of 7.3 has been found in the cytosol of rat liver. The activity of this protease increased in N-2-fluorenylacetamide-induced hepatoma as well as in fetal liver. It has been purified from normal liver and hepatoma about 200-fold. Its mol wt is estimated by gel filtration to be about 200,000 in each tissue. The protease activity is unaffected by chymostatin, pepstatin, soybean trypsin inhibitor, and p-chloromercuribenzoate. Antipain, leupeptin, tosyl-L-lysine chloromethyl ketone, and phenylmethylsulfonyl fluoride inhibit the protease activity. This protease appears to be a serine protease. (Author abstract) (22 Refs)

43. EVALUATION OF TRANSFORMATION ASSAYS USING C3H 10T1/2 CELLS FOR USE IN SCREENING (MEETING ABSTRACT).

Schechtman LM, Lubet RA, Kouri RE, Sivak A, Tu AS
Microbiological Associates, Bethesda, MD, 20816
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

The C3H 10T 1/2 C1 8 (10 T 1/2) cell transformation system is being evaluated independently and simultaneously in two laboratories for its utility, reliability and reproducibility as a predictive in vitro screening test for potential chemical carcinogens. Eleven known chemicals were tested using a standard protocol in the absence of exogenous metabolic activation. The polycyclic hydrocarbon carcinogens 3-methylcholanthrene, 7,12-dimethylbenz(a)anthracene, benzo(a)pyrene (BaP) and dibenz(a,h)anthracene induced Type II and Type III foci, while the non-carcinogens phenanthrene and anthracene were non-transforming. The direct-acting agents N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), ethyl methanesulfonate and N-acetoxy-2-fluorenylacetamide (AFAA) induced little or no transformation. The procarcinogenic aromatic amines N-2-fluorenylacetamide and 2-anthramine were not active. Thus the 'standard' assay shows a range of sensitivity, depending upon the specific class of chemicals employed. To overcome such limitations, the assay has been modified by (a) cell synchronization, (b) increasing cells at risk, (c) replating treated cells ('level II transformation'), and (d) supplying exogenous metabolizing activity (eg hepatocytes, S-9). Transformation of 10T 1/2 cells was induced by MNNG and AFAA using modified protocols without a metabolic supplement. Use of an Aroclor-1254-induced rat hepatic S-9 resulted in activation of a variety of chemicals to cytotoxic metabolites. S-9-mediated enhancement of phenotypic transformation has been thus far achieved with BaP. Additional studies employing hepatocytes for metabolic activation are in progress. Validation studies of cell populations derived from Type III foci showed that while most transformed populations grew in soft agarose, their tumorigenic potential was dependent on the strain, age and immunosuppression of host animals used. Efforts are ongoing to assess the efficacy of these different approaches in rendering the 10T 1/2 cell system responsive to diverse classes of procarcinogens and direct-acting carcinogens. Validation of the transformation system is being carried out by testing coded samples. (no Refs)

AMINO ACID ANALOGS AND MODIFIED NUCLEIC ACID CONSTITUENTS

44. A SINGLE-DOSE PROTOCOL FOR AZASERINE INITIATION OF PANCREATIC CARCINOGENESIS IN THE RAT.

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Int J Cancer; 28(5):601-606 1981

Previously, the induction of pancreatic carcinogenesis in the rat using azaserine has involved a multiple-dose treatment protocol. The objective of the present study was to determine the effect of multiple azaserine treatments on pancreatic DNA synthesis and to develop a protocol for a single-dose initiation of pancreatic carcinogenesis by azaserine in the rat. Pancreatic DNA synthesis in young rats, which was determined by measuring the amount of [3H]-thymidine incorporation into DNA, was found to be elevated at 4.3 wk of age and to decrease to a baseline level by 6.3 wk. Treatment of 4-wk-old rats with azaserine resulted in a dose-dependent inhibition of [3H]-thymidine incorporation into both pancreatic and liver DNA. Max inhibition was seen at 10 mg/kg body wt. This inhibition was followed by a gradual return of incorporation to normal values over a 48 hr period. One wk following pretreatment with four weekly injections of azaserine at 30 mg/kg, [3H]-thymidine incorporation into pancreatic and liver DNA was significantly elevated, suggesting that multiple injection protocols cause enhanced DNA synthesis which could have a co-carcinogenic and/or promotional effect. Single-doses of azaserine (10, 30 and 60 mg/kg) given at 7 wk of age caused the appearance of more atypical acinar cell nodules (AACN) than when given at 5 wk of age. The most effective dose was 30 mg/kg. Using alkaline elution, we determined that this response was due to the occurrence of more DNA damage in the 7-wk-old animals. Thus, these results demonstrate a rationale for the use of single-dose initiation protocols in the pancreas. An effective single-dose protocol for induction of AACN in azaserine-treated rats fed semi-synthetic diet is presented. (Author abstract) (28 Refs)

45. RAT ALPHA-FETOPROTEIN IS NOT PRODUCED CONSTITUTIVELY IN MOUSE HEPATOMA X NORMAL ADULT RAT HEPATOCYTES HYBRIDS, NOR IS IT INDUCIBLE BY ETHIONINE TREATMENT (MEETING ABSTRACT).

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Oncodev Biol Med; AbstractsBook,1:P7 1981

We have previously reported that hepatocyte hybridomas can be generated by fusing mouse hepatoma cells with hepatocytes from normal abult rat; such hybrids segregate rat chromosomes, but retain the capacity to secrete one or several rat serum proteins like the normal hepatocyte parent. They actively secrete mouse alpha fetoprotein (AFP), like the parental mouse hepatoma cells, but do not produce rat AFP in sizeable amount. We have now isolated new hybrids clones which differ from the previous ones in having retained a high number of rat chromosomes; however, like the previous hybrids, they do not secrete rat AFP in amount detectable by radioimmunoassay. No stimulation of AFP production could be observed by treating hybrid cells with ethionine, a hepatocarcinogen known to activate AFP production in vivo. In these hybrids, the rat AFP genes, contributed by the adult hepatocyte are thus not activated, although they co-exist with active mouse AFP genes. In the course of this study, we also found that rat hepatoma lines derived from the Reuber H35 hepatoma secrete low amounts of rat AFP; their rate of AFP secretion changes during the growth cycle (it is decreased during the stationary phase), and is not stimulated by ethionine treatment, or by hybridization with AFP-producing mouse hepatoma cells. (no Refs)

46. INHIBITION OF PANCREATIC CARCINOGENESIS BY RETINOIDS IN AZASERINE-TREATED RATS.

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Cancer Res; 42(1):19-24 1982

Chemoprevention by retinoids of the progression of carcinomas induced in rats by azaserine was evaluated. Wistar/Lewis rats were given 15 weekly injections of azaserine, 10 mg/kg, while fed a chow diet; after the completion of carcinogen treatment, they were fed a chow diet supplemented with four different retinoids at the level of 0.5 to 2 mmol/kg diet for 1 yr. The incidence of neoplasms was determined by autopsy and histological study. The incidence of pancreatic carcinoma among a male positive control group (azaserine treated, but not retinoid treated) was 42%. The incidence of pancreatic carcinoma among male rats treated with retinoids was: N-2-hydroxyethylretinamide, 6%; N-4-propionyloxyphenylretinamide, 17%; and retinylidene dimedone, 12%. The incidence in rats fed these three retinoids was significantly (p less than 0.05) below the control group incidence. Thus, these three retinoids appeared to be effective in inhibiting the progression of pancreatic carcinomas in the azaserine-induced model. A similar trend was demonstrated in females, but statistical significance was shown only in rats fed N-2-hydroxyethylretinamide. A fourth retinoid, N-4-carboxyphenylretinamide, was more toxic and less effective in chemoprevention. Since retinoids were fed after exposure to carcinogen, the effect was exerted during the postinitiation phase of carcinogenesis. The ratio of invasive pancreatic carcinomas to localized carcinomas (carcinoma in situ) was clearly higher among non-retinoid-treated rats than among those treated with retinoids. This is consistent with retarded progression in the retinoid-treated groups. (Author abstract) (10 Refs)

47. CELL-STAGE-SPECIFIC ENHANCEMENT BY CAFFEINE OF THE FREQUENCY OF CHROMATID ABERRATIONS INDUCED BY X-RAYS IN NEURAL GANGLIA OF DROSOPHILA MELANOGASTER.

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Mutat Res; 84(1):91-99 1981

The effect of caffeine on chromatid aberrations induced by x-rays in neural ganglia of Drosophila melanogaster was studied. Ganglia were removed from third-instar larvae and treated with colchicine (10(-3) M) to accumulate cells in mitosis. They were then exposed to caffeine (10(-2) M), x-rays (500 R), or both. Caffeine alone produced high rates of chromatid aberrations only when added to cells late in G2 phase or during mitotic prophase. Although caffeine alone did not induce aberrations during S-phase, middle G-phase, or C-mitosis, it did enhance the damage produced by x-rays. This enhancement was similar in all three phases. During S- and G2-phases damage consisted primarily of isochromatid deletions and chromatid exchanges. Treatment during C-mitosis produced all types of chromatid damage. Enhancement of X-ray-induced damage may be due to inhibition of DNA repair mechanisms by caffeine. (25 Refs)

48. BIOCHEMICAL DETERMINANTS IN THE CYTOTOXIC ACTION OF 9-BETA-D-ARABINOFURANOSYLADENINE.

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Diss Abstr Int [B]; 42(4):1420-B 1981

Studies with 9-beta-D-arabinfuranosyladenine (ara-A) have illustrated that there are numerous cell functions which are affected by the nucleoside analog and its metabolities. Although the precise mechanism responsible for the cytotoxicity of this drug is not known, it is presently thought that the nucleoside must first be phosphorylated to the 5'-triphosphate, ara-ATP, which may exert cytotoxicity through potent competitive inhibition (with dATP) for DNA synthesis, partial inhibition of ribonucleotide reductase, or incorporation of ara-AMP, the nucleotide analog, into DNA. The research described here investigated these major biochemical effects of ara-A in Chinese hamster ovary (CHO) cell in order to better define the mechanism of action of the drug. In addition, the effect of 2'-deoxycoformycin (dCF), a potent inhibitor of adenosine deaminase, on the deamination and cytotoxicity of ara-A was studied. The evaluation of ara-A-induced cytotoxicity by quantitation of the total cellular exposure to ara-ATP accounted for the possibility that more than one mechanism of action involving ara-ATP may contribute to the observed cell lethality, including the inhibition of DNA synthesis and incorporation of ara-AMP into DNA. (no Refs)

49. 1-BETA-D-ARABINOFURANOSYLCYTOSINE STIMULATES THYMIDINE INCORPORATION INTO THE DNA OF CONTACT-INHIBITED CELLS.

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Fairchild Center Biological Sciences, Columbia Univ., New York, NY, 10027
Exp Cell Res; 135(2):427-435 1981

In rapidly proliferating cells 1-beta-D-arabinofuranosylcytosine (ara-C) is a potent inhibitor of DNA synthesis whose effect can be irreversible and consequently cytocidal. Whereas thymidine incorporation is greatly reduced in rapidly proliferating cells in the presence of ara-C, contact-inhibited cells, similarly treated, show increased thymidine incorporation by as much as seven-fold This ara-C induced stimulation appears to result from an influence on thymidine utilization rather than increased DNA synthesis. (Author abstract) (20 Refs)

ALIPHATIC HALOGEN COMPOUNDS

50. MUTAGENICITY OF GLYCEROL CHLOROHYDRINS AND OF THEIR ESTERS WITH HIGHER FATTY ACIDS PRESENT IN PROTEIN HYDROLYSATES.

Silhankova L, Smid F, Cerna M, Davidek J, Velisek J
Dept. Biochemistry and Microbiology, Inst. Chemical Technology, 166 28 Prague 6, Czechoslovakia
Mutat Res; 103(1):77-81 1982

Mutagenicity of the glycerol chlorohydrins 3-chloro-1,2-propanediol (3CP) and 1,3-dichloro-2-propanol (1,3DP), and of their esters with palmitic and oleic acids, was tested with strains of Salmonella typhimurium and Escherichia coli. 3CP and 1,3DP caused base substitutions in S typhimurium TA1535 with and without metabolic activation. Metabolic activation in vitro with S9 mix did not influence the mutagenic effect of non-toxic concentrations of the glycerol chlorohydrins, but it led to a strong increase in the amount of mutants with those chlorohydrin concentrations causing strong suppression of background growth without metabolic activation. Difference in the growth of wild-type and repair-deficient strains of E coli was observed only for 1,3DP with S9 mix. Esters of both 3CP and 1,3DP with fatty acids had smaller mutagenic effects than unesterified compounds. (16 Refs)

51. BIOCHEMICAL AND HISTOPATHOLOGICAL CORRELATES OF CHLOROFORM CARCINOGENESIS IN THE MOUSE AND RAT (MEETING ABSTRACT).

Jorgenson TA, Rushbrook CJ, Jones DC
No affiliation given
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

Chloroform was administered to male Osborne-Mendel rats and to female B6C3F1 mice at concentrations of 0 (negative controls), 200, 400, 900, or 1800 ppm in the drinking water for 24 mo. Matched control groups of both species received a vol of water identical to that consumed by the corresponding 1800 ppm groups. At this writing, the animals have been sacrificed and histologic processing of tissues is in progress. Negative control and CHCl(3)-treated rat groups showed typical growth curves, with dose-related decrements in body wt evident throughout the study. Following decreases in CHCl(3)-treated groups during the first 8 wk, rat water consumption values continued to increase slowly, but persistent relative dose-related decrements were evident. No initial treatment-related mortality was seen in the rats. Survival at 24 mo was 12, 25, 29, 60, 66 and 54% for the negative control, 200, 400, 900, and 1800 ppm, and matched control rat groups, respectively. In the mice, early mortality, apparently associated with rejection of the CHCl3 soln, resulted in survival values of 99, 94, 74, and 76% for the 200, 400, 900 and 1800 ppm groups, respectively, at 3 wk. Subsequent mortality was 16% or less for all mouse groups. Except for acclimation effects during the first 2-3 wk, body wt for the treated mouse groups were generally within 10% and water consumption within 25% of negative control values. Tissue changes in decedents have been similar in treated and control groups, both in rats and mice. (no Refs)

52. FAILURE OF CHLOROFORM TO INDUCE CHROMOSOME DAMAGE OR SISTER-CHROMATID EXCHANGES IN CULTURED HUMAN LYMPHOCYTES AND FAILURE TO INDUCE REVERSION IN ESCHERICHIA COLI.

Kirkland DJ, Smith KL, Van Abbe NJ
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Food Cosmet Toxicol; 19(5):651-656 1981

Mutagenicity of chloroform in Escherichia coli strains WP2p and WP2uvrA-p was tested using both plate incorporation and liquid pre-incubation. In addition, ability of chloroform to induce sister-chromatid exchanges (SCE) in human lymphocytes in the presence of S-9 rat-liver microsomes was tested. Chloroform did not induce reversions in WP2p or WP2urvA-p in either of the assays used. In contrast, both positive control chemicals used (N-methyl-N'-nitro-N-nitrosoguanidine and 2-aminoanthracene) were mutagenic. Benzo-(a)pyrene at concentrations up to 10 ug/ml induced significant increases in SCE in human lymphocytes in the presence or the absence of S-9, whereas chloroform (25-400 ug/ml) plus S-9 induced a significant increase in SCE in cells from the same donor only at the 50-ug/ml dose. Whereas the positive control gave reasonable dose-response trends [correlation coefficient (r) 0.995 and 0.782 with and without S-9, respectively], this was not the case for chloroform (r = 0.206). Failure of chloroform to induce any type of mutagenic event in vitro raises questions in relation to prediction of cancer risk. (19 Refs)

53. THE HEALTH EFFECTS AND ECOLOGICAL SIGNIFICANCE OF CHLORINE RESIDUALS IN WATER.

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Chemosphere; 10(10):1163-1175 1981

Effects of chlorine residuals and organic compounds in drinking water and aquatic environments, particularly direct toxicity and/or carcinogenicity to human and aquatic life, are reviewed. Significant correlations between surface water chlorination and cancer mortality rates have been shown in humans. Elevated rates of bladder, rectal, colon, and gastrointestinal cancers in humans served by chlorinated water from the Mississippi River have been demonstrated. The use of chlorinated surface waters in Ohio was associated with stomach cancer in males and females, and with bladder cancer in males. Chloramine has been shown to be an extremely weak mutagen; involvement of DNA is suggested, since DNA-repair mutants are sensitive to the agent. In uremic patients, shortened RBC survival and hemolysis have been attributed to chlorinated tap water used in hemodialysis. Effects on aquatic life of chlorine residuals are reviewed. While more than 300 chlorinated organic compounds have been identified in chlorinated potable waters, cooling waters, and sanitary effluents, relatively little is known about their ecological effects. Laboratory research using animal models should focus on the chloramines and their effects on health. (65 Refs)

54. MORTALITY STUDY OF DRY CLEANERS EXPOSED TO PERCHLOROETHYLENE (MEETING ABSTRACT).

Brown DP, Kaplan S
No affiliation given

Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

A retrospective cohort mortality study was conducted to examine the long term effects from occupational exposure to perchloroethylene (PCE). This investigation was undertaken as a result of animal experiments that indicated that PCE was a carcinogen in mice. The study cohort consisted of 1,597 individuals who were employed for at least one yr before 1960 in dry cleaning shops where the primary solvent was PCE and who had no known previous occupational exposure to trichloroethylene or carbon tetrachloride. Eligible study cohort members were identified from four union locals. These records were supplemented by solvent history information on union local members shops. Of the 1,597 workers in the study, 1,058 (66.2%) were alive as of September 30, 1977, 285 (17.8%) were known dead and 254 (15.9%) were of unknown vital status. The study cohort was 64.5% female, and race was only known for deceased individuals. It was estimated that between 20-50% of the cohort was black. Conclusions regarding the risk of mortality for most causes of death are limited because of incomplete vital status ascertainment and lack of information on race. However, based on the results, cancer of the colon, which accounted for 11 observed deaths and approx 6.8 expected deaths, appears to be the cause of death most likely to have resulted from occupational exposure to PCE. It is recommended that the vital status follow-up of this cohort be updated. In addition, more accurate information on race should be added to the file before any further analysis is conducted. (no Refs)

55. ALPHA-FETOPROTEIN: CELLULAR ORIGIN OF A BIOLOGICAL MARKER IN RAT LIVER UNDER VARIOUS EXPERIMENTAL CONDITIONS.

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Virchows Arch [Pathol Anat]; 393(1):9-26 1981

Alpha1-fetoprotein (AFP) was detected by serological, light and electron microscopic methods in various experimental models. These included (a) liver regeneration after partial hepatectomy or CCl4 intoxication (mouse and rat); (b) liver intoxication by high doses of N-nitrosomorpholine (NNM) and chemical induction of hepatomas (rat). AFP levels varied greatly according to the animal species and strains used. Low and high AFP-producing species and strains were distinguished. In liver regeneration after hepatectomy or CCl4 intoxication, cellular AFP was found in the cytoplasm of hepatocytes. In NNM-intoxicated livers, elevated AFP levels were associated with proliferation of canalicular epithelial cells in which AFP was localized. In early stages of hepatocarcinogenesis, significant AFP increase occurred after high-dose carcinogen feeding and AFP was also localized in proliferating canalicular epithelial cells. On low-dose NNM feeding, no cellular AFP was detected unless hepatomas had developed. At the stage of malignant conversion, distinct AFP staining and non-AFP staining hepatocellular carcinomas appeared in livers. (Author abstract) (69 Refs)

56. ESTIMATION OF GENETIC RISKS OF ALKYLATING AGENTS: VI. EXPOSURE OF MICE AND BACTERIA TO METHYL BROMIDE.

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Mutat Res; 84(1):1-9 1981

The relationships between dose 14C-labeled methyl bromide (MB) and degree of alkylation of DNA, and mutagenic response, and between the degree of alkylation of Hb and of DNA were studied. In Escherichia coli, MB had high toxicity (LD50: 6-8 milliM x hr) and low mutagenic efficiency (1 mutation/10(8) surviving bacteria/milliM x hr), which was predicted by a high s factor. CBA mice received 80 or 37 uCi MB by inhalation or 21.6 uCi/kg by ip injection. DNA alkylation in the liver and spleen was lower than that predicted by alkylation of Hb by factors of 200 and 20, respectively. In vitro DNA and Hb reactivities also predicted higher in vivo DNA alkylation than was obtained. This indicates that when Hb alkylation is used to evaluate quantitative risk, a correction factor must be used. For MB, the correction factor is less than 1. (14 Refs)

57. CARCINOGENICITY OF INHALED 1,2-DIBROMOETHANE IN RATS TREATED WITH DISULFIRAM (MEETING ABSTRACT).

Wong LC, Winston JM, Hong CB
Midwest Research Institute, Kansas City, MO
Toxicologist; 1(1):130 1981

A chronic inhalation study of ethylene dibromide (EDB) was conducted in Sprague Dawley rats. The study consisted of four groups of rats receiving control air and control diet, 20 ppm of EDB and control diet, control air and 0.05% of disulfiram (DS) in the diet, and 20 ppm of EDB and 0.05% of DS in the diet, over a period of 18 mo. Rats receiving 20 ppm of EDB showed high mortality and an increase in tumor incidences in mammary glands, spleen, adrenals, liver, kidneys, and sc tissues. A combination of 20 ppm of EDB and 0.05% DS in the diet caused earlier deaths and high mortality rate, decreases in body wt gain, food consumption, Hb, hematocrit and RBC counts in rats. This combination of EDB and DS treatment also caused early development and high incidences of tumors in liver, spleen, kidneys, adrenals, thyroids, lungs, mesentary and mammary tumors. In addition, 90% of male rats that received a combination of EDB and DS treatment had testicular atrophy. Addition of DS treatment caused early deaths and high mortality rate, and promoted not only the tumor incidences in various organs and tissues in both male and female rats, but also the testicular atrophy in rats. (no Refs)

58. THE INFLUENCE OF DISULFIRAM AND OTHER INHIBITORS OF OXIDATIVE METABOLISM ON THE FORMATION OF 2-HYDROXYETHYL-MERCAPTURIC ACID FROM 1,2-DIBROMOETHANE BY THE RAT.

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Biochem Pharmacol; 30(21):2983-2987 1981

The mercapturic acid derivative, N-acetyl-S-2-hydroxyethyl-L-cysteine, is a major metabolite of 1,2-dibromoethane in vivo. This compound can be formed via two pathways, both involving a potentially dangerous reactive intermediate. One way involves the intermediacy of bromoacetaldehyde, formed by microsomal oxidation, followed by loss of hydrogen bromide. The second pathway, direct conjugation of 1,2-dibromoethane with glutathione, gives rise to S-2-bromoethyl glutathione. Using several inhibitors of microsomal mixed function oxidases, it was found that under these conditions about 10% of the mercapturic acid derivative formed via direct conjugation. Disulfiram, an inhibitor of aldehyde dehydrogenases, but also of microsomal oxidation, also markedly inhibits the excretion of the mercapturic acid, after a dministration of a single high dose (1 g/kg) or upon chronic treatment with a low dose (50 mg/kg). The inhibitory effect is max after 10 days of chronic treatment. Administration of large amounts of 1,2-dibromoethane (greater than 0.20 nmole/rat) following a single lower dose of disulfiram (125 mg/kg) also leads to a lower excretion of mercapturic acid metabolite, a phenomenon associated with a decrease in cytochrome P-450 levels. From these results it is concluded that the enhanced carcinogenic effect of the combination disulfiram (chronic)/1,2-dibromoethane is not caused by bromoacetaldehyde, since its formation is completely inhibited under these conditions, but by S-2-bromoethyl-glutathione, although a role for 1,2-dibromoethane itself cannot be excluded. (Author abstract) (27 Refs)

59. MUTAGENICITY AND CYTOTOXICITY OF HALOETHANES AS STUDIED IN THE CHO/HGPRT SYSTEM.

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Mutat Res; 90(2):183-191 1981

Mutagenic and cytotoxic effects of ethylene dibromide (EDB), ethylene bromochloride (EBC), and ethylene dichloride (EDC) as quantified in the Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl transferase mammallian cell gene mutation assay are reported. All haloethanes tested exhibited mutagenic activity in the presence or absence of S9, in the order EDB greater than EBC greater than EDC. When tested as direct-acting agents, EDM, EBC, and EDC reduced cell survival to 50% at approx 3, 6, and 50 mM, respectively. Cell survival decreased with further increases in haloethane concentration. Cell survival dropped exponentially over a treatment time of 24 hr, but the mutagenic activity attained a max at approx 5 hr. The haloethanes were 5-25x more toxic in the presence of S9 than in its absence. S9-induced toxic metabolites were also more mutagenic to the cells. Such increased toxicity is NADPH-dependent. (22 Refs)

POLYHALOGENATED RING COMPOUNDS INCLUDING INSECTICIDES

60. SEX DIFFERENCE IN THE ACQUISITION OF GAMMA-GLUTAMYL TRANSPEPTIDASE (GGT) POSITIVE FOCI IN THE LIVER OF SPRAGUE-DAWLEY RATS FED POLYCHLORINATED BIPHENYLS (PCB) (MEETING ABSTRACT).

Cihla HP, Weltman RH, Pitot HC, Norback DH
Department of Pathology, Middleton Memorial Veterans Hospital, Madison, WI
Toxicologist; 1(1):137 1981

The potential of a PCB mixture (Aroclor 1260) or a pure congener, 2,3,6,2',3',6',-hexachlorinated biphenyl (HCB), to induce gamma glutamyl transpeptidase positive hyperplastic foci and hepatocellular carcinoma (HCC) was studied. Serial liver sections (obtained at 9, 12 and 15 mo from male and female rats fed diets containing Aroclor 1260 [100 ppm from 13 mo followed by 50 ppm], HCB [100 ppm for 9 mo followed by intermittant exposure at 50 ppm] or control feed) were histochemically assayed for GGT activity and histologically assessed. No enzymatic or histopathic alteration was noted with HCB feeding. Progressive change was induced with Aroclor-1260 feeding and is described. At 9 mo, both male and female rat liver showed centrilobular hypertrophy that was not associated with GGT activity. Only females developed hyperplastic foci that were homogenously GGT positive (MD equals 133 um, mean diameter of the enzyme-altered foci). Males showed a higher number of diffuse, GGT-positive areas (MD equals 79 um). All controls were negative. At 12 mo, females showed an increase in number and size of GGT foci (MD equals 245 um) and female controls yielded a background incidence of GGT-positive areas (MD equals 73 um). By 15 mo, both sexes yielded hyperplastic foci with homogeneous GGT activity, while females showed progression to neoplastic nodules and HCC heterogeneous for GGT activity (female control MD equals 44 um, female experimental MD equals 1157 um). No fibrotic changes were noted. (no Refs)

61. AROCLOR 1254-INDUCED INTESTINAL METAPLASIA AND ADENOCARCINOMA IN THE GLANDULAR STOMACH OF F344 RATS.

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Cancer Res; 41(12):5052-5059 1981

Ingestion of diets containing Aroclor 1254, a mixture of polychlorinated biphenyls, for 2 yr led to a dose-related increase in the incidence of focal lesions in the glandular stomachs of male and female F344 rats. The incidence of stomach lesions was 6% in control specimens and in specimens from rats fed a diet containing 25, 50, or 100 ppm Aroclor 1254, the incidences of stomach lesions were 10, 17, and 35, respectively. The majority of gastric lesions in treated rats were histologically identified as intestinal metaplasia characterized by an architecture resembling that of intestinal crypts and particularly by goblet cells, which stained with Alcian blue and periodic acid-Schiff reagent. Adenocarcinomas were found in six specimens. Most (88%) of the lesions were located in the pyloric region of the glandular stomach. No multiple lesions were observed among 47 control specimens examined; however, 9 cases of multiple lesions were observed in 30 lesion-containing specimens from Aroclor 1254-treated rats. Although the exact relationship between gastric intestinal metaplasia and adenocarcinoma remains to be established, they commonly coexist and may share initiating mechanisms. (Author abstract) (46 Refs)

62. MUTAGENIC EFFECT OF TRICHLORFON AND DIMETHOATE ON MOUSE MYELOCYTES IN VIVO.

Nehez M, Selypes A, Scheufler H
Kozegeszsegtani es Jarvanytani Intezet, Szegedi Orvostudomanyi Egyetem, Szeged, Hungary
Egeszsegtudomany; 25(3):262-266 1981

The mutagenic effects of trichlorfon (TF; 1 x 405 mg/kg ip) and dimethoate (1 x 20 or 1 x 60 mg/kg ip) were studied in male CFLP mice after 24 and 48 hr. Significant differences were found in the number of aberrant cells 24 and 48 hr after treatment with TF, and 24 and 48 hr after treatment with 60 mg/kg dimethoate. The number of aberrant cells 48 hr after TF treatment was 22/200 vs 5/200 in the controls (p less than 0.01). Numerical aberration was found in 1/200 cases (0/200 in the controls), chromatid gap in 21/200 (4/200 in the controls), and break in 0.200 (1/200 in the controls). The number of aberrant cells 48 hr after treatment with 60 mg/kg dimethoate was 51/200 (vs 6/200 in the controls): numerical aberration was found in 7/200 cases (vs 0/200 in the controls), chromatid type aberration in 35 (4 in the controls), and chromosome type aberration (acentric fragment and deletion) in 9 (in the controls). The findings suggest the possibility of the mutagenic effect of both substances. (26 Refs) (In HUN)

63. SPONTANEOUS TUMORS IN THE ADRENAL MEDULLA OF LONG-EVANS RATS (MEETING ABSTRACT).

Wilson-Martino NA, McCarthy KJ, Mankes RF, Benitz KF
Institute of Experimental Pathology and Toxicology, The Albany Medical, College Albany, NY, 12208
Toxicologist; 1(1):153 1981

On the basis of reported longevity and low incidence of spontaneous neoplastic processes, 360 Long-Evans rats from Blue Spruce Farms were fed the organophosphate pesticide NTN 8629 at dietary concentrations of 0.5 and 25ppm for 2 yr. Although no adverse affects, directly attributable to the administration of NTN 8629, were elicited, the incidence of 16.4% (or 57/348) of neoplastic processes in the adrenal medulla was far greater than expected in this strain of rats. Of these 57 cases, 38 were selected for detailed pathologic characterization (on the basis of technical considerations) and evaluated for: wt, laterality, local invasiveness, vascular erosion, peripheral dissemination (tumor emboli), metastases, alveolar pattern, papillary pattern, vasculature, analplasticity, mitotic activity and peripheral compression. Of the 38 tumors, 30 were benign pheochromocytomas while 8 pheochromoblastomas showed signs of malignancy with local invasiveness, vascular erosion, intra-vascular, tumor emboli, local and distant metastases. Only 1 malignant neoplasm was found in a female. The remaining 7 were all in males. The most malignant case was found in a male control with local spread and distant metastases to the lungs and both kidneys. Of the 30 benign tumors, 15 were found in males and an equal number in females. (no Refs)

64. LIVER CARCINOGENESIS: THE ROLE FOR SOME CHEMICALS OF AN EPIGENETIC MECHANISM OF LIVER-TUMOR PROMOTION INVOLVING MODIFICATION OF THE CELL MEMBRANE.

Williams GM
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Food Cosmet Toxicol; 19(5):577-583 1981

A number of chemicals, including phenobarbitals, DDT, and polychlorinated biphen yl, are hepatocarcinogenic in mice and rats after prolonged exposure; they lack genotoxic action and have been suggested to be epigenetic carcinogens. Because several of these chemicals enhance the effect of genotoxic carcinogens under conditions in which they are not themselves carcinogenic, they are probably of the promoter class of epigenetic carcinogens. Mechanism of promotion may involve (1) completion of conversion of partially transformed cells to full neoplastic cells, or (2) inhibition by the promoter of intercellular communication. The first mechanism has been demonstrated in skin-tumor promoters (phorbol esters and teleocidin B), whereas the latter mechanism has been demonstrated in studies in which tumor promoters inhibited intercellular communication in fibroblast- and liver-cell cultures. Inhibition by DDT of metabolic cooperation between hepatocytes and adult rat-liver epithelial-thioguanine-resistant mutant cells is described. The theory that tumor promoters interfere with transmission of regulatory factors from normal to spontaneously transformed cells is consistent with the dose-response characteristics of epigenetic promoter hepatocarcinogens. (37 Refs)

BENZENE DERIVATIVES

65. BUTYLATED HYDROXYTOLUENE PRETREATMENT REDUCES CYTOTOXICITY AND COVALENT BINDING OF AFLATOXIN B1 IN PRIMARY HEPATOCYTE CULTURES (MEETING ABSTRACT).

Salocks CB, Hsieh DP, Byard JL
Department of Environmental Toxicology, University of California, Davis, CA
Toxicologist: 1(1):108 1981

Primary cultures of adult rat hepatocytes were used to characterize the effect of butylated hydroxytoluene (BHT) pretreatment on the cytotoxicity and metabolism of a cytotoxic dose of aflatoxin B1 (AFB1). Male Sprague-Dawley rats were divided into two groups of four each, and fed either a control diet or one containing 0.5% BHT. After ten days, hepatocytes were prepared and cultured in chemically-defined, hormone-supplemented medium. After 20-22 hr in culture, 0.12-0.15 ug of [14C] AFB1 were added to dishes containing 2.5 x 10(6) cells. Medium was removed from sets of three cultures at 1/2, 1, 2, 4, 6, 10, and 24 hr thereafter, and extracted with chloroform. Cells were precipitated with 5% TCA and washed exhaustively with organic solvents. After 10 hr, control cells converted 59% of the AFB1 to aqueous metabolites, while 15% was bound covalently. During the same intervals, cells from BHT-fed rats produced 69% aqueous metabolites, and only 6% was bound covalently. AFB1-induced cytotoxicity was much greater in cells from control rats, as evidenced by release of lactate dehydrogenase (LDH) into the medium. Thirty-one hr after addition of AFB1, LDH levels in media from control cells av 1036+/-169 units/ml, while media from BHT-pretreated cells contained only 350+/-45 units/ml. BHT reduces cytotoxicity by apparently increasing the output of relatively nontoxic, water-soluble metabolites and decreasing the output of activated metabolites which covalently bind to macromolecules. Based on results from this in vitro model, we predict the BHT will also protect against AFB1-induced acute toxicity and carcinogenicity in vivo. (no Refs)

66. EFFECTS OF BUTYLATED HYDROXYANISOLE ON THE ARYL HYDROCARBON HYDROXYLASE OF RATS AND MICE.

Yang CS, Sydor W, Martin MB, Lewis KF
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Chem Biol Interact; 37(3):337-350 1981

The effects of butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) on the aryl hydrocarbon hydroxylase (AHH) activities in the liver, lung and skin of rats and mice have been studied to examine the possible mechanisms of the anticarcinogenic actions of these compounds. Both compounds inhibit the hydroxylase activities of hepatic microsomes and nuclei, with BHA a more potent inhibitor than BHT. The AHH of lung microsomes is inhibited to a lesser extent by BHA and BHT than that of the liver. The AHH activities of both liver and lung microsomes become less susceptible to the inhibition after pretreatment of the animals with 3-methylcholanthrene (MC) or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) but phenobarbital (PB) pretreatment does not produce such an effect. In skin homogenates, however, the AHH activities of control rats and mice are not inhibited by BHA and BHT. The only skin sample which is inhibited by BHA and BHT is that from TCDD-pretreated mice. It has been established that the extent of inhibition with different samples is related to the concentration of BHA in the incubation but not to the amounts or specific activities of microsomes used. Double reciprocal plots suggest that BHA exerts a mixed inhibition on the hydroxylase of liver microsomes with Ki of 7.7 uM. Analysis of the metabolites of benzo[a]pyrene (BP) shows that BHA inhibits the formation of various metabolites uniformly without changing the regioselectivity of the enzyme system. The mechanism of inhibition has also been studied with a reconstituted AHH system consisting of cytochrome P-450 (P-450), reductase and phospholipid. The system with P-450 isolated from PB-induced microsomes is inhibited to a much greater extent than that with MC-induced P-450. The results indicate that the inhibitory action of BHA is dependent on the species of the animal, tissue types and treatment with inducers. (Author abstract) (42 Refs)

67. METABOLISM AND MACROMOLECULAR BINDING OF THE CARCINOGEN MICHLER'S KETONE IN RATS.

Struck RF, Shih TW, Johnston TP, Kirk MC, Hill DL
Kettering-Meyer Lab., Southern Res. Inst., Birmingham, AL, 35255
Xenobiotica; 11(8):569-577 1981

Studies on the metabolism of 14C-Michler's ketone (4,4'-bis-(dimethylamino)[carbonyl-14C]benzophenone) in rats have revealed that this carcinogen is subject to demethylation, ring-hydroxylation and N-acetylation after adjacent methyl groups have been removed. As identified by mass spectral analysis, microsomal metabolites are the mono-, di-, tri- and tetra-demethylated derivatives. The major metabolites appearing in the bile are the di- and tri-demethylated derivatives and the N-acetylated tetra-demethylated compound; minor metabolites, tentatively identified, are the ring-hydroxylated derivatives of di- and tri-demethylated Michler's ketone and of N-acetylated tri- and tetra-demethylated Michler's ketone. The major urinary metabolite is tentatively identified as a ring-hydroxylated derivative of N-acetylated, di-demethylated Michler's ketone; a minor urinary metabolite lacks the hydroxyl group. Injection of 14C-Michler's ketone into rats resulted in the irreversible binding of radioactivity to liver proteins. When the rats were pretreated with phenobarbital, this binding was increased and extended to proteins of some other tissues and to DNA and RNA of liver and DNA of kidney. (Author abstract) (13 Refs)

68. SAFROLE: ITS METABOLISM CARCINOGENICITY AND INTERACTIONS WITH CYTOCHROME P-450.

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Food Cosmet Toxicol; 19(5):657-666 1981

This review of safrole metabolism is aimed at elucidating the importance of the allyl moiety and the methylenedioxy group in the mechanism of carcinogenesis. It includes studies concerning safrole carcinogenicity, interactions of safrole with cytochrome P-450, inhibition of mixed-function oxidase activity by safrole, ligand complex formation with cytochromes P-450 and P-448, and hemoprotein formation by safrole and isosafrole. Ligand complexing and covalent binding of reactive intermediates with the heme and protein moieties, respectively, of cytochrome P-450, may be fundamental to the mechanism of safrole carcinogenesis. Structural and functional properties of the cytochrome are substantially changed by this binding, which, since ribosomes are attached to the endoplasmic reticulum at cytochrome P-450, may be associated with loss of ribosomes known to occur following treatment with safrole or other carcinogens. Chemical carcinogenesis is associated with increases in hepatic cytochrome P-448 and simultaneous loss of cytochrome P-450 activity and could, through loss of ribosomes, result in impairment of glycoprotein synthesis and thus contribute to malignant transformation by epigenetic mechanism. Therefore, of the two functional groups of safrole, the allyl group has been shown to be associated with mutagenicity, and the methylenedioxy moiety to be associated with changes to cytochrome P-450 and possibly with epigenetic aspects of carcino genicity. (84 Refs)

DRUGS, COSMETICS, DETERGENTS AND OTHER COMMERCIAL MATERIALS

69. EXPERIMENTAL LESIONS INDUCED IN RATS BY POLYVINYL CHLORIDE (PVC) COMBUSTION FUMES.

Dessy E, Faa G, Calatri S, Bucarelli A
II Cattedra di Anatomia e Istologia Patologica, Universita di Cagliari, Cagliari, Italy
Boll Soc Ital Biol Sper; 57(11):1278-1281 1981

The effect of pure polyvinyl chloride (PVC) powder combustion fumes was studied in 14 adult white Wistar rats. Forced inhalation of wood combustion fumes was given to eight control rats. The forced inhalation was administered for 1 hr every day during 30-180 days. The rats were sacrificed approx 1 yr after the end of the experiment. While they were exposed to fumes animals were irritable, aggressive, dehydrated, and lost wt. Most significant histological findings were in lung (metaplasia of bronchial epithelium), and liver (enlargement of sinusoidal bed, and activation of Kupffer cells). Animals treated for an extended period of time had marked alopecia of the neck and back, and histologically sebaceous gland hyperplasia. Two rats had three sc tumors, histologically diagnosed as adenocarcinomas (neck, and mammary sites). (7 Refs) (In ITA)

70. CARCINOGEN BIOASSAYS OF SEVERAL PHTHALIC ACID DERIVATIVES AND RELATED COMPOUNDS (MEETING ABSTRACT).

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National Toxicology Program, National Cancer Institute, Bethesda, MD, 20205
Toxicologist; 1(1):130 1981

Carcinogenesis bioassays have been conducted with select phthalic acid derivatives and di(2-ethylhexyl)adipate. Test animals were F344 rats and B6C3F1 mice. Only those esters containing the 2-ethylhexanol moiety were considerably carcinogenic. Hepatocellular carcinomas occurred in a dose related fashion in high- and low-dose male and female rats and mice which received diets containing the di-(2-ethylhexyl)phthalate. Di(2-ethylhexyl)adipate was not carcinogenic in rats; however, increased incidences of liver tumors were detected in both male and female mice. In separate studies, increased tumor incidences were not detected in male or female Wistar or Sherman rats fed diets containing di(2-ethylhexyl)phthalate for 104 wk. (no Refs)

71. STUDIES ON THE MECHANISM OF DENATURATION OF CYTOCHROME P-450 BY CYCLOPHOSPHAMIDE AND ITS METABOLITES.

Gurtoo HL, Marinello AJ, Struck RF, Paul B, Dahms RP
Dept. Experimental Therapeutics, Roswell Park Memorial Inst., Buffalo, NY, 14263
J Biol Chem; 256(22):11691-11701 1981

In vivo depression of rat hepatic microsomal mixed function oxidase by cyclophosphamide, an important anti-cancer and immunosuppressive agent was investigated. Essentially exclusive metabolism-dependent binding to microsomal proteins of 14C from [4-14C]cyclophosphamide, compared with 3H from [chloroethyl-3H]cyclophosphamide, suggests the binding of the metabolite acrolei n. Of the various metabolites and analogs of cyclophosphamide tested, only acrolein and 4-hydroxycyclophosphamide (which releases acrolein in soln) caused denaturation of microsomal cytochrome P-450 in vitro; this denaturation was identical with that produced by sulfhydryl reagents. Of the chemicals tested, only those containing either a free amino group (except lysine) and/or a free sulfhydryl group (eg semicarbazide, cysteine, glycine, glucosamine) effectively blocked (40-80%) the binding of 14C as well as protected against acrolein-induced denaturation of cytochrome P-450. These data further suggested interaction of cyclophosphamide metabolite with free amino and/or free sulfhydryl groups in proteins. However, comparison with [3H]aflatoxin B2a which interacts with free protein amino groups via the formation of Schiff bases, clearly attributed the preferential binding of 14C to cysteine sulfhydryl groups in these proteins. Studies on chemical models derived from reaction between acrolein and cysteine also supported this suggestion. When microsomes isolated from incubations metabolizing [4-14C]cyclophosphamide were subjected to gel electrophoresis, the major radioactive band detected by autoradiography was associated with a cytochrome P-450 band at 55,000 daltons, the major band induced by phenobarbital in the rat. These results strongly point to the possibility that acrolein is the cyclophosphamide metabolite responsible for the depression of the mixed function oxidase activities. Acrolein most likely produces this effect by alkylation of the sulfhydryl group(s) in the active site of cytochrome P-450. (Author abstract) (59 Refs)

72. MUTAGENICITY PATTERNS RESULTING FROM THE REACTION OF NITRITE WITH ICR-170.

de Flora S, Zanacchi P, Camoirano A, Bennicelli C
Inst. Hygiene, Univ. Genoa, Via Pastore 1, 16132 Genoa, Italy
Mutat Res; 103(1):13-17 1982

ICR-170, 2-methoxy-6-chloro-9-(3-[ethyl-2-chloroethyl] aminopropylamino) acridine.2HCl reacted with nitrite in an acidic environment to form a mutagenic derivative. Suitable soln of sodium nitrite were preincubated, either separately or mixed together, with 5 ml of human gastric juice or 0.15 M NaCl adjusted to various pH values. After 60 min at 37 C, 1 ml of 0.2 M phosphate-buffered saline, pH 7.4, was added. The resulting mixtures (0.5 ml/plate) were assayed in the plate incorporation test using various Salmonella his- strains. All the strains except TA1535 were reverted by ICR-170. TA1537 was most sensitive, a finding typical for acridine derivatives. Mutagenicity of TA1537 and of the other positive strains (TA 1538, TA98, and TA100) was increased by rat liver S9 fractions. The metabolic effect was less pronounced than previously reported for the same compound lacking an ethyl group (ICR-191). Direct frameshift activity of ICR-170 decreased in all positive strains after its reaction with nitrite. Such an activity was replaced by an S9-requiring mutagenic response in TA1538, TA98, and TA100; the response correlated with the amounts of both ICR-170 and nitrite. The study suggests that nitrosation of ICR compounds occurs at the only site where ICR-170 and ICR-191 are different, ie, at the terminal nitrogen of the nitrogen-mustard moiety. (10 Refs)

73. EFFECTS OF PROLONGED CHEMICAL TREATMENT WITH CYCLOPHOSPHAMIDE AND 6-MERCAPTOPURINE IN THE DOMINANT LETHAL TEST SYSTEM.

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Div. Toxicology, Food and Drug Admin., Washington, DC, 20204
Mutat Res; 90(2):193-199 1981

The effects of prolonged exposure (5 daily ip injections/wk for 10 wk) to cyclophosphamide (CP) and 6-mercaptopurine (6MP) were quantified using the dominant lethal assay. A dose-dependent reduction in fertility occurred in male rats treated with either compound. After final injection, male rats were housed with two virgin females/wk for 2 wk. The 10.0 mg/kg dose of CP caused a reduction in total implants per pregnant female and an increase in number of dead implants per female and of females with two or more dead implants. Negative results were obtained for all fertility criteria examined in 6MP-treated animals, except for a significant decrease in total number of implants per pregnant female at the 25 mg/kg level. Treatment with triethylene-melamine, the positive control compound, caused a significant decrease in number of total implants per pregnant female and a significant increase in the value for dead implants per total implants. (12 Refs)

74. BASE-PAIR SUBSTITUTION HOTSPOTS IN GAG AND GCG NUCLEOTIDE SEQUENCES IN ESCHERICHIA COLI K-12 INDUCED BY CIS-DIAMMINEDICHLOROPLATINUM (II).

Brouwer J, Van de Putte P, Fichtinger-Schepman AM, Reedijk J
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Proc Natl Acad Sci USA; 78(11,part2):7010-7014 1981

Cell killing and mutation induction by cis- and trans-PT(NH3)2CL2 in Escherichia coli were examined by studying forward mutagenesis in the lacI gene in cells with different repair capacities. Survival experiments showed that repair-proficient cells were slightly more sensitive for the cis isomer than for the trans isomer, whereas repair-deficient RecA and UvrB cells were extremely sensitive only for the cis compound. cis-Pt(NH3)2Cl2 induced mutagenesis in both wild-type cells and RecA cells but not in UvrB cells; whereas no detectable mutagenesis was induced by treatment with the trans compound. Examination of the nature of the mutations induced by cis-PT(NH3)2Cl2, by using the LacI system, revealed that base-pair substitutions leading to nonsense mutants are only induced in wild-type cells, suggesting that the int act products of both the uvrB and the recA gene are necessary for the repair responsible for this type of mutagenesis. Investigation of the nonsense mutants reveals that 70% of these mutations result from GC - TA or GC - AT substitutions at sites where the guanine is part of a GAG or GCG sequence. These results are discussed in relation to existing theories on the interaction between Pt compounds and DNA. A model for Pt-DNA adducts, leading to base-pair substitutions, is proposed. (Author abstract) (50 Refs)

75. SOME CARCINOGENIC, MUTAGENIC, AND BIOCHEMICAL PROPERTIES OF PLATINUM ANTITUMOR COORDINATION COMPLEXES AND OF S-VINYL- AND S-ETHYLHOMOCYSTEINE.

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Diss Abstr Int [B]; 42(3):998-B 1981

It is known that cis-dichlorodiammineplatinum(II) (DDP), cis-dichlorobis(cyclopentylamine)platinum(II) (DCP), and the three stereoisomeric forms of dichloro-1,2-diaminocyclohexaneplatinum(II) (DDCP) and of sulfato-1,2-diaminocyclohexaneplatinum(II) (SHP) each induced lung adenomas in A/JAX mice, while cis-DDP also initiated skin papillomas in CD-1 mice. Cis-DCP and cis-dichlorobis(pyrrolidine)platinum(II) induced sarcomas at the injection site in rats. Each of the above complexes was mutagenic for Salmonella typhimurium TA100, and the mutagenicity of the SHP and DDCP complexes was highly dependent on the stereoconfiguration of the 1,2-diaminocyclohexane ligand. No quantitative correlation of mutagenicity or tumorigenicity with electrophilic reactivity (as determined by reaction with DNA) or reported antitumor activity was found for the DDP, DDCP, and SHP complexes. The mutagenic and carcinogenic properties of S-vinylhomocysteine (vinthionine) were examined in relation to those of S-ethylhomocysteine (ethionine) to test a hypothesis that vinthionine might be a proximate carcinogenic form of ethionine. (no Refs)

76. DETECTION OF DNA SINGLE-STRAND BREAKS PRODUCED DURING THE REPAIR OF DAMAGE BY DNA-PROTEIN CROSS-LINKING AGENTS.

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Cancer Res; 42(1):145-149 1982

In this investigation, the combination of 1-beta-D-arabinofuranosylcytosine and hydroxyurea was used to inhibit the polymerase step of DNA excision repair. The DNA single-strand breaks (SSB), which accumulated in the presence of these agents, were measured by alkaline elution. With this approach, DNA SSB were detected in normal human fibroblasts after exposure to trans-platinum(II)diamminedichloride, formaldehyde or potassium chromate. These agents all share the common feature in that they induce DNA-protein cross-links in mammalian cells. In the case of trans-platinum(II)diamminedichloride or formaldehyde, the frequency of these SSB was markedly less in excision-deficient xeroderma pigmentosum cells. With chromate, a high level of SSB was induced in both normal and xeroderma pigmentosum cells; these results indicate that chromate damage to DNA is repaired by a mechanism different than the classical excision pathway since xeroderma pigmentosum cells responded normally. Several other agents were investigated with this approach, and no SSB were detected with nickel sulfate, 12-O-tetradecanoylphorbol-13-acetate or asbestos fibers in the presence or absence of the polymerase inhibitor. This approach was found to be a very sensitive method to detect DNA excision repair. (Author abstract) (21 Refs)

77. INDUCTION OF DEOXYRIBONUCLEIC ACID DAMAGE IN HELA S3 CELLS BY CYTOTOXIC AND ANTITUMOR SESQUITERPENE LACTONES.

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Dept. Pharmaceutical Technology and Biochemistry, Technical Univ. Gdansk, 80-952 Gdansk, Poland
Biochem Pharmacol; 30(21):3005-3007 1981

Effects of parthenolide, 1,10-epoxyparthenolide, alatolide, eupatoriopicin, vernolepin, elphantopin, and costunolide on DNA synthesis and cellular growth were tested. Incubation of HeLa S3 cells with 202 uM parthenolide resulted in an almost complete inhibition of DNA synthesis in subcellular systems derived from the cells. Addition of the cytoplasmic fraction from untreated cells did not reverse inhibition, suggesting that interference with DNA templates plays a major role. All of the lactones induced DNA damage in HeLa cells at 35 and 75x their ED50 doses. The lactones did not cause DNA breaks in isolated DNA. Results supported the theory that alkylation of DNA is a molecular basis for biological activity of sesquiterpene lactones. (16 Refs)

78. DAMAGING EFFECTS OF FOURTEEN CHEMOTHERAPEUTIC DRUGS ON MOUSE TESTIS CELLS.

Meistrich ML, Finch M, Da Cunha MF, Hacker U, Au WW
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Cancer Res; 42(1):122-131 1982

The harmful effects of 14 chemotherapeutic drugs on spermatogenesis in the mouse have been evaluated by studies of testicular cell killing and morphological and genetic damage produced. Male mice were given drugs as single injections at various doses up to the toxic levels. Prednisone and 6-mercaptopurine produced little or no cytotoxicity. All other drugs tested killed differentiated spermatogonia. Of these, methotrexate, cyclohexylchlorethylnitrosourea, cis-platinum, and mechlorethamine did not show significant stem cell killing. Bischlorethylnitrosourea, chlorambucil, 5-fluorouracil, mitomycin C, actinomycin D, and procarbazine showed some stem cell killing. Triethylenethiophosphoramide (thio-TEPA) was the only drug in this group which killed large numbers of stem cells. Only 5-fluorouracil and cis-platinum killed spermatocytes, and only cis-platinum killed spermatids. Several drugs induced chromosome breaks in treat ed spermatocytes. thio-TEPA was effective in inducing chromosome translocations in treated spermatocytes and probably also in spermatocytes which originated from surviving treated stem cells. It had been our hypothesis that the cytotoxic effects of these drugs on mouse testicular stem cells would correlate with the duration of azoospermia observed in patients. This was shown not to be the case. Thus, the cytotoxic effects of single injections of single chemotherapeutic agents on the mouse testis did not appear to be predictive of which drugs will cause long-term azoospermia in humans. (Author abstract) (50 Refs)

79. DNA-DAMAGE IN HUMAN CELLS TREATED WITH THE CLOSELY RELATED ALKYLATING AGENTS PEPTICHEMIO, M-L-SARCOLYSIN AND MELPHALAN.

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Eur J Cancer Clin Oncol; 17(9):991-996 1981

In vitro experiments were performed on human peripheral WBC to compare DNA repair synthesis induced by peptichemio (a multipeptide complex containing m-L-sarcolysin), m-L-sarcolysin and melphalan. The peptide bound m-L-sarcolysin gave rise to max DNA repair synthesis at a concentration interval between 1 x 10(-5) and 3 x 10(-5) M as opposed to a concentration interval of 3 x 10(-4) to 1 x 10(-3) M for melphalan. The peptide bound m-L-sarcolysin induced DNA repair synthesis at similar molar concentrations to m-L-sarcolysin alone. The difference between melphalan on one hand, and m-L-sarcolysin and peptichemio on the other hand, may reflect a more rapid uptake of the latter substances. Inhibition of 3H-uridine incorporation in human peripheral lymphocytes supports this hypothesis. The frequency of sister chromatid exchanges in human fibroblasts was significantly higher after treatment with m-L-sarcolysin compared to melphalan, a finding which also indicates that these chemically closely related substances modify the cellular DNA differently. When DNA repair synthesis was induced by UV light and methyl-methane-sulfonate (a monofunctional alkylating agent), no additional DNA repair synthesis was induced, if peptichemio, m-L-sarcolysin or melphalan was added. These results indicate that the repair of lesions induced by melphalan peptichemio, UV-light and methyl-methane-sulfonate is mediated by at least one common controlling enzyme. (Author abstract) (17 Refs)

80. MITOMYCIN C- AND STREPTOZOTOCIN-INDUCED MOTILITY AND NUMERICAL SPERM VARIANTS IN MICE.

Fiesor G, Elansari OA
Dept. Biomedical Sciences, Western Michigan Univ., Kalamazoo, MI, 49008
Mutat Res; 90(3):287-295 1981

Mitomycin C, a cross-linking mutagen and clastogen, and streptozotocin, a point mutagen, were observed to decrease sperm motility and sperm count in treated male HA (ICR) mice and in their F1 progeny. These effects may result from gene mutations and/or chromosomal aberrations. (15 Refs)

81. RELATIONSHIP BETWEEN IN VIVO MITOMYCIN C EXPOSURE, SISTER CHROMATID EXCHANGE INDUCTION AND IN VITRO MITOGENIC PROLIFERATION. I. DEVELOPMENT OF MURINE SPLENIC CELL SYSTEM.

Mann PL, Kern DE, Kram D, Schneider EL
Oncology Center, Johns Hopkins Univ. Medical Center, Room 1-27, Baltimore, MD, 21205
Mech Ageing Dev; 17(2):195-201 1981

In vivo administration of mitomycin C (MMC) to C57BL/6J mice induced a rapid, initial suppression (24 hr post injection) of in vitro mitogenesis. This was followed by inhibition of phytohemagglutinin and concanavalin A mitogen responses that were no longer mitogen concentration independent (48-72 hr post injection). This can be seen in the mitogen concentration-response curves for the three mitogens, phytohemagglutinin, concanavalin A and lipopolysaccharide. By 144 hr post injection, the dose-response curves and magnitude of the responses had returned to approx control (untreated) levels. This approach provides a model system for the functional assessment of in vivo cellular damage by MMC. (Author abstract) (11 Refs)

82. RELATIONSHIP BETWEEN IN VIVO MITOMYCIN C EXPOSURE, SISTER CHROMATID EXCHANGE INDUCTION AND IN VITRO MITOGENIC PROLIFERATION. II. EFFECT OF AGING ON SPLEEN CELL MITOGENESIS AND SISTER CHROMATID EXCHANGE INDUCTION.

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Oncology Center, Johns Hopkins Univ. Medical Center, Room1-127, Baltimore, MD, 21205

Mech Ageing Dev; 17(2):203-209 1981

In vivo administration of mitomycin C (MMC) produces an increase in both the frequencies of sister chromatid exchange (SCE) as well as inhibition of in vitro mitogenic responses. At low concentrations of MMC (2 mg/kg) spleen cell suspensions from both young and old mice showed similar patterns of mitogen inhibition and increased SCE frequencies. At high MMC concentrations (5 mg/kg) significant differences between young and old responses were observed. Spleen cells from young animals displayed mitogen-inhibition curves which plateaued with increasing doses of MMC, while the cells from old animals displayed a continuing increase in mitogenic inhibition. MMC-induced SCE frequencies revealed a complementary pattern: increasing SCE frequencies as a function of MMC concentration in young spleen cells while SCE levels plateaued in old spleen cell populations. The results of these studies suggest (1) that an inverse relationship exists between sister chromatid exchange induction and mitogenic response, (2) that cells from older animals may have an increased sensitivity to high levels of DNA damage (5 mg/kg MMC), and (3) that this sensitivity may be expressed functionally by increased inhibition of in vitro mitogenic responses. (Author abstract) (18 Refs)

83. STUDIES ON MICRONUCLEI TIME RESPONSE AND ON THE EFFECTS OF MULTIPLE TREATMENTS O F MUTAGENS ON INDUCTION OF MICRONUCLEI.

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Mutat Res; 90(2):165-173 1981

Specific effects revealed by the micronucleus assay were investigated. Micronuclei time responses for five mutagens were examined and micronucleus frequencies observed after single or multiple (5) treatments were compared for nine mutagens. Max frequencies of micronucleated RBC (MNEs) occurred at 24 hr post treatment for mitomycin C and triethylenemelamine, and 30 hr post treatment for busulfan, 6-mercaptopurine, and vincristine. Single and five-treatment schedules were equally effective in detecting alkylating agents and spindle poisons. The five-treatment schedule was more sensitive for detection of anti-metabolites. Most MNEs induced by a single treatment with alkylating agents and with anti-metabolites were type BS. After five treatments with these agents, MNEs classified as type RS were increased in a dose-dependent fashion. Types BL and RL were rarely observed with these agents; in the single- and five-treatment schedules using spindle poisons these types were seen with increasing frequency. (16 Refs)

84. EFFECT OF RETINOIDS ON PLATING EFFICIENCY, SISTER-CHROMATID EXCHANGE (SCE) AND MITOMYCIN-C-INDUCED SCE IN CULTURED CHINESE HAMSTER CELLS.

Sirianni SR, Chen HH, Huang CC
Dept. Biology, Niagara Univ., Niagara, NY, 14109
Mutat Res; 90(2):175-182 1981

Cytogenetic effects of five retinoids, all-trans-retinol (ROL), all-trans-retinoic acid (RA), all-trans-retinal (RAL), all-trans-retinyl acetate (RAc), and Ro. 10-9359 TMMP ethyl retinoate (TMMP), on cultured Chinese hamster cell line V79 were investigated. The five retinoids differed in ability to decrease plating efficiency. None induced sister-chromatid exchange (SCE) and none had an effect on mitomycin-C-induced SCE. RAL was the most potent reducer of plating efficiency, followed in decreasing order by ROL, RAc, RA and TMMP. The results discount a cellular mechanism of retinoids based on mitotic recombination. (27 Refs)

85. INHIBITION OF BLEOMYCIN-INDUCED DNA BREAKAGE BY SUPEROXIDE DISMUTASE.

Galvan L, Huang CH, Prestayko AW, Stout JT, Evans JE, Crooke ST
Dept. Pharmacology, Baylor Coll. Medicine, Houston, TX, 77030
Cancer Res; 41(12):5103-5106 1981

Inhibition of bleomycin (BLM)-induced DNA breakage by superoxide dismutase (SOD) has been reported and presumed to be due to its removal of the superoxide free radicals generated by BLM in the presence of iron(II). We have studied the possibility that the inhibitory effect might result from DNA-binding of SOD. The effect of copper-zinc SOD on BLM-induced DNA degradation was investigated using the PM-2 DNA fluorescence technique. PM-2 DNA was incubated with BLM in the presence or absence of native and heat-inactivated copper-zinc SOD as determined by the epinephrine autoxidation method. The concentrations of SOD required to inhibit 50% PM-2 DNA degradation for the native and the inactivated SOD were 100 and 120 ug/ml, respectively. Analysis of the reaction mixture by agarose gel electrophoresis confirmed the absence of DNA degradation by BLM in the presence of either form of SOD. PM-2 DNA was shown to bind native or inactivated SOD by Sephadex G-100 column chromatography, fluorescence-quenching studies, and agarose gel electrophoresis. Thus, these results indicate that SOD is able to bind to PM-2 DNA and inhibit BLM-induced degradation independently of its free radical-scavenging activity. The inhibition was more effective against BLM than other compounds which degrade PM-2 DNA. This suggests that SOD may bind to BLM-binding and/or BLM degradation sites in PM-2 DNA, and the observed inhibition is unrelated to its effects on free radicals. (Author abstract) (19 Refs)

86. CYTOTOXIC AND MUTAGENIC EFFECTS OF STERIGMATOCYSTIN ON CULTURED CHINESE HAMSTER CELLS.

Noda K, Umeda M, Ueno Y
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Carcinogenesis; 2(10):945-949 1981

Cytotoxicity and mutagenicity of sterigmatocystin (STC) on cultured Chinese hamster cells were investigated in the presence and absence of a metabolic activation system. STC, when applied directly to V79 cells, was cytotoxic and induced 8-azaguanine-resistant mutations in a dose- and time-dependent manner. Effects of STC were enhanced markedly by 1%, 5%, or 20% S15 (polychlorinated biphenyl-induced rat liver microsomes) and other cofactors. In the presence of 1% S15, STC concentration required to induce cytotoxicity was approx 20x less than that required when S15 was applied directly; 1% STC was more cytotoxic and more mutagenic than either 5% or 20% STC. Analysis on the basis of equitoxic levels demonstrated that there was little difference in the degree of mutagenicity induced by direct treatment with STC and treatment with STC in the presence of S15. The effects of STC were enhanced in proportion to the duration of the treatment period. Treatment for shorter periods, however, was more effective than that for longer periods. The decreased effectivness was not attributable to instability of STC. (21 Refs)

87. MUTAGENIC ACTIVITY OF ANTIBIOTICS ALONE AND IN CONJUNCTION WITH ALKANESULFONATES.

Prasad PR, Prasad AB
Mutagenesis and Cytogenetics Lab., Dept. Botany, L. S. Coll., Muzaffarpur-842001, India
Mutat Res; 84(1):83-90 1981

The effects of antibiotics [ampicillin, neomycin (NM), and furadentine] and alkylating agents [ethyl methanesulfonate, methyl ethanesulfonate, and methyl methanesulfonate (MM)] on Phaseolus vulgaris were studied individually and in combination. Chlorophyll mutations occurred more oft en with combined treatment than with single-agent treatments. NM and MM produced the highest mutation rates among their respective groups. (16 Refs)

88. CHANGES IN THE PROTEINS OF TUMOR CELL PLASMA MEMBRANES OF MICE TREATED WITH POLYENE ANTIBIOTIC AND CYCLOPHOSPHAMIDE.

Oksman AIa, Shneider MA, Eremeeva AA, Karel'skaia NP, Tereshin IM
All-Union Res. Technological Inst. Antibiotics and Medicinal Enzymes, Leningrad, USSR
Antibiotiki; 26(9):692-694 1981

To evaluate the mechanism of potentiation of cyclophosphamide (CP) by polyene antibiotics, random-bred albino mice bearing Ehrlich ascites carcinoma were treated with CP (15 mg/kg, im) and/or with levorin (LV: 75 mg/kg, iv). The drugs were administered for 7 days, starting on day 2 of tumor transplantation. Inhibition of tumor growth in the animals treated with CP in combination with LV was 60-70% greater than that in the animals treated with CP alone. Electrophoretic analysis of plasma membranes of the tumor cells showed summation of the changes in the membrane protein composition induced by CP and by LV. (7 Refs) (In RUS)

89. LUNG INJURY AND REPAIR IN THE MOUSE FOLLOWING CYCLOPHOSPHAMIDE (MEETING ABSTRACT).

Hakkinen PJ, Whiteley JW, Witschi HP
University of Tennessee, Oak Ridge, TN, 37830
Toxicologist; 1(1):140 1981

Treatment of BALB/c mice with a single ip injection of cyclophosphamide produces a dose-dependent (100-300 mg/kg) increase in lung hydroxyproline content within 3 wk. Using 14C-thymidine incorporation as an index of lung cell proliferation, it was found that treatment with either 100 mg/kg or 200 mg/kg cyclophosphamide resulted in an increase in thymidine incorporation with three peaks occurring at 4 days (100 mg/kg) or 7 days (200 mg/kg) (7 x control), 11 days (approx 3.5 x control) and 16 days (approx 2.5 x control) after injection. Studies of the time course of hydroxyproline content indicate that the major increase in hydroxyproline content occurs between days 9 and 16 after injection. Exposure of mice to 70% oxygen for either days 1-10 or days 11-21 following 200 mg/kg cyclophosphamide results in a potentiation of cyclophosphamide-induced hydroxyproline content only when oxygen is administered on days 1-10. These results indicate that a second agent such as oxygen can potentiate cyclophosphamide-induced pulmonary fibrosis if exposure occurs at a critical time following initial injury. (no Refs)

90. DIFFERENTIAL INDUCIBILITY OF CHROMOSOME ABERRATIONS AND SISTER-CHROMATID EXCHANGES BY INDIRECT MUTAGENS IN VARIOUS MAMMALIAN CELL LINES.

Ikeuchi T, Sasaki M
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Mutat Res; 90(2):149-161 1981

A variety of mammalian cell cultures were examined for inducibility of chromosomal aberrations (CA) and sister chromatid exchanges (SCE) by the indirect mutagens cyclophosphamide (CP), dimethylnitrosamine (DMN), and benzo(a)pyrene (BP). Sixteen cell lines were examined for response to CP. All rat ascites hepatoma cell lines showed a significant increase in frequencies of both SCE and CA in a dose-dependent manner. Several rat esophageal tumor cell lines showed an extremely high sensitivity to CP, with significant yields of SCE and CA obtained at much lower concentrations compared to other cell lines. Seven cell lines were examined for their responsiveness to DMN. AH66-B, R1 and R3 cells, which showed a significant response to CP, were also sensitive to DMN in induction of CA. SCE frequency increased only slightly, however. Of the four cell lines studied for BP sensitivity, GHE cells showed the highest response to BP; frequencies of both SCE and CA were increased up to 3.8-and 6.9x. AH66-B and B-13 were moderately sensitive. HE2144 was almost insensitive but showed slightly increased frequency of SCE. (28 Refs)

91. MUTAGENICITY SCREENING OF ANESTHETICS FOR FISHES.

Yoshimura H, Nakamura M, Koeda T
Second Assay Div., Natl. Veterinary Assay Lab., 1-15-1 Tokura, Kokubunji-shi, Tokyo 185, Japan
Mutat Res; 90(2):119-124 1981

Anesthetics used in the handling of commercially valuable fish were studied for genetic toxicity. Eugenol, phenthiazamine, and tricaine were tested for mutagenicity in the rec assay with Bacillus subtilis strains M45 (rec-) and H17 (rec+), and in the reverse mutation assay with Salmonella typhimurium strains TA100, TA98, TA1535, TA1537, and TA1538. No DNA damage was detectable for any of the compounds in the repair assay. In the mutagenicity studies, phenthiazamine gradually increased the revertant colonies in strains TA100, TA98 and TA1537 in the presence of S9 mix in a dose-dependent fashion. Neither eugenol or tricaine were mutagenic in any strain in the presence or absence of S9 mix. (14 Refs)

92. A CARCINOGENICITY STUDY IN MICE OF A BETA-ADRENERGIC ANTAGONIST, PRIMIDOLOL: INCREASED TOTAL TUMOR INCIDENCE WITHOUT TISSUE SPECIFICITY.

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Toxicology; 21(4):279-290 1981

Carcinogenicity of the beta-adrenergic blocker primidolol hydrochloride (B-PR) was tested in CD-1 mice. B-PR was administered in the diet at daily doses of 12.5, 25, and 50 mg/kg body wt. A sex-related pattern of tumor incidence was discovered after 18 mo of treatment. Female mice had significantly more tumors in the top dose group (48%) than did controls (24%). In male mice the situation was reversed, with 30% of animals in the high dose group carrying tumors vs 48% in controls. No organ-specific effect was observed for B-PR tumorigenicity in female mice. Total tumor count may be an unreliable indicator of carcinogenic risk. (34 Refs)

93. REPAIR OF PSORALEN-TREATED DNA BY GENETIC RECOMBINATION IN HUMAN CELLS INFECTED WITH HERPES SIMPLEX VIRUS.

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Cancer Res; 41(12):5033-5038 1981

Herpes simplex virus type 1 was treated with 4,5',8-trimethylpsoralen (psoralen) plus near-UV light in order to produce lesions (monoadducts and DNA cross-links) in the viral DNA. Human fibroblasts were infected by damaged virus under conditions in which either a single virus particle or several particles entered a given cell, and the fraction of virus-producing cells was determined. This fraction was significantly greater for multiply infected cells than for singly infected cells, indicating that the psoralen lesions are repaired more efficiently in the presence of homologous, damaged DNA (multiplicity reactivation). Evidence is presented that herpes simplex virus may code for functions which participate in its own repair, both during multiplicity reactivation and during repair which occurs in singly infected cells: (a) host cells deficient in repair of lesions induced by psoralen (xeroderma pigmentosum) or the DNA cross-linking agent mitomycin C (Fanconi's anemia) exhibited normal levels of multiplicity reactivation of psoralen-treated herpes virus; (b) while xeroderma pigmentosum cells have been previously shown to be deficient in repair of psoralen-treated adenovirus under conditions of single infection, herpes virus is repaired at near normal levels in these same cells. Recombination levels between genetically marked pairs of herpes viruses were found to increase after treatment of the parental viruses with psoralen, suggesting that psoralen damage stimulates genetic recombination. This stimulation provides convincing evidence for a repair pathway in which genetic recombination between damaged viral genomes can lead to the production of viable virus. (Author abstract) (28 Refs)

94. THE INFLUENCE OF PROCARBAZINE (MIH) ON THE INDUCTION OF PROPHAGE LAMBDA IN ESCHERICHIA COLI K12 AND TOXIC EFFECTS ON SALMONELLA TYPHIMURIUM.

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Mutat Res; 90(3):247-254 1981

Procarbazine, a hydrazine derivative active against various malignancies, was found to lead to the formation of weakly mutagenic hydrogen peroxide at concentrations of 8-12 mg/plate in the Escherichia coli prophage lambda induction assay. No mutagenic effect was observed at equal concentrations in Ames test strains TA98 and TA100 of Salmonella typhimurium. (19 Refs)

95. REVIEW OF THE HEPATIC RESPONSE TO HYPOLIPIDAEMIC DRUGS IN RODENTS AND ASSESSMENT OF ITS TOXICOLOGICAL SIGNIFICANCE TO MAN.

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Food Cosmet Toxicol; 19(5):585-605 1981

Hypolipidemic agents produce in rodents a hepatic response, characterized by hepatomegaly, proliferation of smooth endoplasmic reticulum, and a marked increase in the number of peroxisomes and changes in the peroxisomal structure and enzyme composition, as well as liver carcinomas. An overview is presented of biochemical, histochemical, histologic, and ultrastructural changes induced in the liver by these agents. Studies concerning the significance of peroxisome proliferation are stressed, and data are critically assessed to ascertain the extent to which drug-induced changes in the rodent liver are relevant in man. Chemically unrelated hypolipidemic compounds that cause both hepatic peroxisome proliferation and liver carcinomas in rats or mice include clofibrate, nafenopin, tibric acid, and phthalate esters. One indication of the importance of peroxisome proliferation in the development of liver cancer in rodents is that, at low doses, when peroxisome proliferation is absent or minimal, liver tumors do not occur. In addition, hypolipidemic drugs exert differential effects on the activities of hepatic peroxisomal enzymes. Striking increases in the activities of enzymes involved in fatty acid oxidation overshadow the small increases in the activities of catalase and certain oxidase enzymes. It is suggested that the bioavailability of catalase in the liver peroxisomes of rodents treated with hypolipidemic drugs is insufficient to detoxify injurious peroxide concentrations resulting from enhanced activity of hydrogen-peroxide-generating enzymes. Thus, liver cells may be exposed to the cytotoxic or DNA-damaging potential of hydrogen peroxide, which could lead to development of neoplasms. Absence of a peroxisomal response in man coupled with differences in the way rodents and humans handle lipoprotein remnants bound to liver cells make it unlikely that chronic administration of hypolipidemic drugs present a liver-cancer risk in man. (93 Refs)

96. TOXICOLOGICAL IMPLICATIONS OF HEPATIC PEROXISOME PROLIFERATION IN RODENTS: POSSIBLE ROLE OF OXYGEN RADICAL TOXICITY IN HYPOLIPIDEMIC DRUG-INDUCED CARCINOGENESIS (MEETING ABSTRACT).

Reddy JK, Warren JR
Northwestern University Medical School, Chicago, IL
Toxicologist; 1(1):131 1981

The hepatomegaly induced by the hypolipidemic drugs and phthalate ester plasticizers is characteristically associated with a marked increase of peroxisomes in the cytoplasm of liver cells of rats, mice and hamsters. Peroxisomes contain catalase, several H2O(2)-generating oxidases, carnitine acetyltransferase, as well as enzymes involved in the beta- oxidation of long-chain fatty acids. The activities of these enzymes in liver are elevated in association with peroxisome proliferation. To evaluate the implications of persistent peroxisome proliferation, chronic toxicity studies were undertaken. To date, clo fibrate, nafenopin, Wy-14,643, BR-931, tibric acid and methyl clofenapate, 6 structurally different peroxisome proliferators, were found to be hepatocarcinogenic in rats and/or mice. None of these compounds caused detectable mutagenic activity in the Salmonella/microsome assay or produced DNA damage in the lymphocyte [3H] thymidine incorporation asssay. The lack of mutagenicity of these compounds strongly suggests that the carcinogenicity may be related directly to peroxisome proliferation. The sustained increase in liver cell peroxisome population appears to cause an excessive generation of H2O2 as a result of increased H2O(2)-generating peroxisomal oxidases and elevated peroxisomal beta-oxidation of fatty acids. The H2O2 thus generated may react with superoxide radical to form hydroxyl radical. The rate of production of these highly toxic oxygen radicals, including singlet excited oxygen formation, and their cumulative effect on DNA, may determine the relationship between peroxisome proliferation and hepatocarcinogenicity in rodents chronically exposed to peroxisome proliferators. (no Refs)

97. THE EFFECT OF DISULFIRAM ON THE CARCINOGENICITY OF 3,2'-DIMETHYL-4-AMINOBIPHENYL IN SYRIAN GOLDEN HAMSTERS AND RATS.

Fiala ES, Weisburger JH, Katayama S, Chandrasekaran V, Williams GM
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Carcinogenesis; 2(10):965-969 1981

Species differences in 3,2'-dimethyl-4-aminobiphenyl (DMAB) carcinogenicity, which induces mostly bladder tumors in Syrian hamsters and intestinal and breast tumors in rats, were investigated. Groups of male Syrian golden hamsters received sc injections of DMAB weekly for up to 22 mo (total av cumulative dose 555 mg) either alone or simultaneously with disulfiram in the diet. At the tolerated dose of disulfiram (2.5 mg/kg), the overall tumor yield induced by DMAB alone was not affected, but the number of small intestine tumors was reduced and the appearance of bladder and colon cancers was delayed. In two groups of male Charles River rats, weekly sc injection of DMAB (20 mg/kg) for 37 wk (total av cumulative dose 289 or 241 mg) induced primarily intestinal cancers. As in hamsters, addition of disulfiram to the diet of the second group reduced the incidence of small intestine cancers but resulted in the appearance of a small number of bladder cancers. DMAB-treated rats also developed in situ prostatic carcinoma, regardless of whether they were treated with or without disulfiram. (19 Refs)

98. TUMOR PROMOTION IN RAT LIVER (MEETING ABSTRACT).

Herren SL, Pereira MA
U.S. Environmental Protection Agency, Cincinnati, OH
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

An initiation/promotion bioassay using gamma glutamyl transpeptidase (GGTase) positive foci as the endpoint has been developed that can detect the carcinogenic potential of chemical carcinogens. GGTase-positive foci are presumed to be areas of initiated hepatocytes in contrast to the GGTase-positive areas of Zone 1 diffusion observed with compounds such as phenobarbital and saccharin. To evaluate the tumor promoting activity of phenobarbital, rats were administered diethylnitrosamine (DENA), 0.3 mmole/kg, followed by 500 ppm phenobarbital in their drinking water. After six wk of phenobarbital promotion, the rats had an increased incidence of foci as compared to non-phenobarbital treated rats. By 50 wk of phenobarbital promotion, the number of foci in the non-promoted animals equaled the number observed with promotion. This demonstrated that the initiator determined the ultimate number of foci while the promoter decreased the latent period required for the observation of foci. In an experiment to determine the effect of phenobarbital on the stability and progression of GGTase-positive foci, rats received a 2/3 partial hepatectomy, followed 24 hr later by DENA (0.3 mmole/kg). The rats then received 500 ppm phenobarbital in the drinking water for eight wk. After eight wk, half of the rats were continued on phenobarbital and the other half were taken off phenobarbital. The number of foci/cm 2 observed in rats continued on phenobarbital treatment leveled off after 10 wk of continuous promotion approached that observed with continuous phenobarbital promotion, while the number of foci/cm2 in the rats taken off phenobarbital initially decreased. However, 56 wk after the administration of DENA, the number of foci/cm2 from the rats removed from phenobarbital promotion approached that observed with continuous phenobarbital promotion, although the size of the foci from the rats on continuous promotion was larger. After 81 wk, all six (100%) of the rats on continuous promotion had liver tumors while only three of six (50%) rats removed from promotion had tumors. Therefore, continuous promotion by phenobarbital not only decreased the latent period for the appearance of foci, but also increased the size of DENA initiated foci as well as ultimately increasing the incidence of liver tumors. (no Refs)

99. CARCINOGENESIS OF ROOFING ASPHALTS, PITCH AND ULTRAVIOLET LIGHT (MEETING ABSTRACT).

Niemeier RW, Moss CE, Thayer PS, Menzies KT, VonThuna P
No affiliation given
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

The tumorigenicity to mouse skin of volatile components of roofing asphalts and coal tar pitches has been investigated in an 18-mo experimental program. The main factorial experiment involved 32 groups of 50 mice each. The experimental variables were: male mice of two strains (CD-1 and C3H/HeJ); four initial roofing materials (asphalt, Types I and III; coal tar pitch, Types I and III); two temperatures of generation of volatile fume materials (232 and 316 C); and exposure to simulated sunlight vs the absence thereof. Treatment with condensed volatiles and light was done twice weekly. Additional groups included: a combination treatment (alternate weekly application of 316 C volatiles from Type III asphalt and Type I coal tar pitch); a positive control (benzo(a)pyrene, with and without sunlight); and negative solvent and sunlight controls. With the asphalt volatiles, there was a pronounced effect of temperature of preparation on tumorigenesis, the 316 C preparation being the more active. Pitches did not show this effect, but since the 316 C preparations were applied at lower concentrations and showed tumorigenicity equivalent to that of the 232 C preparations, the former are inferred to have higher specific activity. The combination treatment group showed effects, as might be expected from the individual activities of the two 316 preparations used, without evidence of additivity or synergism. Simulated sunlight had an inhibitory effect more on the rate of appearance of tumors than on the final tumor incidence. In some cases, there was little inhibition, but no enhancement. (no Refs)

100. COMPARISON OF THE MUTAGENICITIES OF FOSSIL FUELS.

Pelroy RA, Sklarew DS, Downey SP
Dept. Biology, Pacific Northwest Lab., Richland, WA, 99352
Mutat Res; 90(3):233-245 1981

Mutagenicity of several shale oils as either unfractionated or partially purified mixtures was tested in the Ames assay system. Only the basic, basic tar, and neutral tar solvent fractions were mutagenic. Most of the mutagenic activity recovered from the Paraho and Livermore shales and the solvent refined coal process II heavy distillate were localized in basic and neutral tars (60-75% for the shale oils and greater than 90% for the coal distillate). More than 90% of mutagenic activity in the corresponding Sephadex LH-20 fractions was found in the methanol fractions. For the less active shale oils, Occidental and Geokinetics, the distribution of mutagens was approx equal between basic and tar fractions. Compared to the unfractionated crude synfuel materials, recoveries of mutagenic activity appeared greater for solvent fractions than for LH-20 fractions. Mutagenicity of the tested shale oils, estimated from genetic activity of both crudes and chemical fractions derived from the crudes, ranged over approx one order of magnitude. (15 Refs)

101. MORTALITY STUDY OF CHEMICAL PLANTS IN THE KANAWHA VALLEY REGION OF WEST VIRGINIA (MEETING ABSTRACT).

Leet TL
No affiliation given
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmen tal and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

The mortality experience of Union Carbide employees at three chemical plants in the Kanawha River Valley region of West Virginia will be evaluated in a study jointly conducted by the National Institute for Occupational Safety and Health (NIOSH) and the Union Carbide Corporation. These plants have produced many chemicals, including acrylonitrile, ethylene oxide, polycyclic aromatic hydrocarbons (PAH), vinyl resins, and pesticides. A company-sponsored proportionate mortality study based on 819 deaths known to Union Carbide found excess proportions of multiple myeloma and cancer of the kidney and CNS. Initial analyses will evaluate the validity of the apparent excesses as well as evaluate all other cause-specific mortality. Further analyses will test the epidemiologic association between 1) ethylene oxide exposure and leukemia and 2) PAH exposure in the coal hydrogenation process and cancer of the respiratory system, urogenital system, and skin. The study cohort includes approx 44,000 employees who were ever employed by Union Carbide in the Kanawha Valley between January 1, 1940 and December 31, 1978. Demographic and work history data have been coded, keypunched, and computerized for 10,000 active and 34,000 former employees. Vital status ascertainment has been initiated and death certificates are being collected for 6,800 (estimated) deceased employees. (no Refs)

102. DERMAL CARCINOGENESIS BIOASSAYS OF SEVERAL COMPONENTS OF PHOTOCURABLE COATINGS (MEETING ABSTRACT).

Peterson LG, DePass LR, Maronpot RR, Weil CS
Bushy Run Research Center, Union Carbide Corporation, Pittsburgh, PA, 15213
Toxicologist; 1(1):154 1981

Photocurable coatings are generally mixtures of monomers, crosslinkers, oligomer and photoinitiator. Such mixtures are used as coatings and in the production of inks and adhesives. Several important components of photocurable coatings were tested for dermal tumorigenic activity by repeated application to the skin of mice. The substances tested were 2-ethylhexyl acrylate (2-EHA) and methylcarbamoyloxyethyl acrylate (MCEA) (monomers); neopentyl glycol diacrylate (NPGDA), ester diol-204-diacrylate (EDDA) and penta-erythritol tri(tetra)acrylate (PETA) (crosslinkers); di-sec-butoxyacetophenone (DBAP) (a photo-initiator); acrylated polycaprolactone-based urethane in 20% 2-EHA, acrylated polyether polyol/isophorone diisocyanate urethane and acrylated polycaprolactone-Hylene W urethane in 30% 2-EHA (oligomers). For each bioassay, 40 C3H/HeJ male mice were dosed 3 x weekly on the dorsal skin for their lifetime with a 'max tolerated dose' of the test agent. Two negative control groups received acetone (diluent) only. A positive control group received methylcholanthrene (MC). NPGDA and 2-EHA showed significant tumorigenic activiti ty with tumor yields of 8 and 6 tumor-bearing mice (3 and 2 malignancies), respectively. EDDA and DBAP had questionable tumorigenic activity with 1 sc hemangioma and 1 papilloma, respectively. The MC group had 34 mice with carcinomas and 2 additional mice with papillomas. MCEA had no tumorigenic activity but resulted in early mortality. No skin tumors in the treatment area were observed in the other groups. Additional studies will be neccesary to elucidate possible relationships between structure and tumorigenic activity for the acrylates. (no Refs)

103. CARCINOGEN BIOASSAY OF DI(2-ETHYLHEXYL)PHTHALATE (MEETING ABSTRACT).

Douglas JF, Hartwell MV
National Toxicology Program, National Cancer Institute, Bethesda, MD, 20205
Toxicologist; 1(1):129 1981

A carcinogen bioassay of di(2-ethylhexyl)phthalate, the most commonly used plasticizer for polymers, was conducted in rats and mice. The compound was administered po in feed for two yr at 6000 and 12000 ppm to both sexes of F344 rats and at dose levels of 3000 and 6000 ppm to both sexes of B6C3F1 mice. Group sizes were 50 including matched controls. Di(2-ethylhexyl)phthalate induced increased incidence of hepatocellular carcinomas or adenomas in both male and female mice, and it also significantly increased hepatocellular carcinomas or neoplastic nodules in either sex of rats. The chemical also produced atrophy and tubular degeneration of the testes and hypertrophy of anterior pituitary cells in male rats. It was concluded that di(2-ethylhexyl)phthalate was carcinogenic to the F344 rat and the B6C3F1 mouse under the experimental conditions. (no Refs)

104. EFFECTS IN THE MAMMALIAN SPOT TEST: CYCLAMATE VERSUS SACCHARIN.

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Mutat Res; 103(1):43-47 1982

Effects of cyclamate and saccharin (SH) in pigment cells of mouse embryos were compared using the mammalian spot test, an in vivo system for detection of genetic alterations including gene mutations. Embryos of the cross C57Bl/6JHan x T stock, heterozygous for four different recessive coat-color genes, were treated in utero on day 10 post-conception. At this time approx 200 pigment precursor cells are available. Treatment consisted of the cyclamate metabolite cyclohexylamine (CHA; 100-200 mg/kg ip), SH (1 g/kg ip), or the SH impurity orthotoluene sulfonamide (OTS; 1 g/kg po in tragacanth). Results indicated CHA was a weak mutagen, with 5/7 experiments giving positive results (8 spots of genetic relevance among 1,332 mice compared to 1 spot in 1,249 controls). With OTS, at least one color spot was observed in each of three experiments, only one considered significant. Hence, classification of OTS as mutagenic or non-mutagenic is not possible. SH should be considered non-mutagenic because the one color spot among 701 mice did not differ significantly from the spontaneous frequency. On the basis of the mammalian spot test alone, cyclamate must be considered potentially more dangerous than SH if the SH preparation used is free of impurities like OTS. (15 Refs)

105. CHRONIC DERMAL TOXICITY OF EPOXY RESINS. 1: SKIN CARCINOGENIC POTENCY AND GENERAL TOXICITY.

Holland JM, Gipson LC, Whitaker MJ, Eisenhower BM, Stephens TJ
Oak Ridge Natl. Lab., Oak Ridge, TN
Sci Tech Aerosp Rep; 19(20):2818 1981

This report quantifies the cutaneous and systemic response of male and female C3H mice to skin application of selected commercial epoxy resins and amine curing agents, at the max tolerated dermal dose. Resins tested were: diglycidyl ether of bisphenol A (DGEBA); mixtures of the same resins with bis(2.3-epoxycyclopentyl) ether; diglycidyl ether of resorcinol; N,N'-diglycidyl-5,5-dimethylhydantion; diglycidyl ether of neopentyl glycol; A 70:30 mixture of the hydantoin and neopentyl glycol base resins; the amine curing agent methane diamine; and a dutectic mixture of meta-phenylenediamine and DGEBA. A DGEBA manufactured by Union Carbide Corporation in the mid 1970's and assayed for skin carcinogenicity previously was chemically characterized. The results of this analysis are included with the present data for comparison purposes. (no Refs)

106. METABOLISM AND DISPOSITION OF TRIS BP IN THE RAT (MEETING ABSTRACT).

Matthews HB, Nomeir AA
National Institute of Environmental Health Science and National, Toxicology Program Research Triangle Park, NC, 27709
Toxicologist; 1(1):35 1981

The flame retardant chemical tris (2,3-dibromopropyl)phosphate (Tris BP), has been shown to be carcinogenic in laboratory animals. In an effort to provide additional data on the disposition of Tris BP in laboratory animals the oral and dermal absorption, tissue distribution, metabolism and excretion of 14C-labeled Tris BP have been studied in the rat. The results of these studies indicate that Tris BP is readily absorbed from the gastrointestinal tract and absorbed at an appreciable rate from the skin. Following absorption Tris BP is distributed to all the major tissues, but Tris BP derived radioactivity is most concentrated in liver, blood and kidney. Tris BP is readily metabolized and excreted in the form of several polar metabolites in urine and feces and as CO2 in exhaled air. Six metabolites of Tris BP have been isolated and identified from urine and bile. Excretion of unmetabolized Tris BP is negligible. In vitro studies of Tris BP metabolism have demonstrated that enzymes in liver degrade the parent chemical to the same polar metabolites which were isolated and identified from urine and bile. The enzymes responsible for Tris BP metabolism are concentrated in microsomal and soluble portions of liver homogenates and require NADPH and glutathione, respectively, as cofactors for enzyme activity. (no Refs)

107. IN VITRO AND IN VIVO COVALENT BINDING OF THE KIDNEY TOXICANT AND CARCINOGEN TRIS(2,3-DIBROMOPROPYL)-PHOSPHATE.

Soderlund EJ, Nelson SD, Dybing E
Dept. Toxicology, Natl. Inst. Public Health, Postuttak, Oslo 1, Norway
Toxicology; 21(4):291-304 1981

Incubation of 3H-tris(2,3-dibromopropyl)-phosphate (TRIS-BP) with rat liver microsomes led to its activation to products which bound covalently to microsomal protein. The reaction was NADPH-dependent, and boiled microsomes yielded no binding. The reaction could be inhibited by nitrogen; carbon monoxide, which inhibits cytochrome P-450-mediated reactions, also reduced binding rates significantly. SKF 525-A and metyrapone, a selective inhibitor of phenobarbital-inducible cytochrome P-450, inhibited TRIS-BP activation. Alpha-napthoflavone, a selective inhibitor of cytochrome P-448, had little effect. Addition of glutathione and N-acetylcysteine markedly inhibited binding, but ascorbic acid did not. Paraoxon, an esterase inhibitor, and 1,1,1-trichloropropene-2,3-epoxide and cyclohexene oxide also were without effect. Rat kidney microsomes were capable of activating TRIS-BP to 8% of the level achieved by rat liver microsomes. Administration of TRIS-BP to rats resulted in considerable binding to kidney proteins, with lesser amounts detected in liver and very little in muscle proteins. Liver microsomes activated TRIS-BP to bind to DNA in vitro, but kidney microsomes did not. (31 Refs)

108. MUTAGENICITY OF COSMETICS INGREDIENTS LICENSED BY THE EUROPEAN COMMUNITIES.

Gocke E, King MT, Eckhardt K, Wild D
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Mutat Res; 90(2):91-109 1981

Cosmetic ingredients allowed by the guidelines of the Council of the European Communities (27 July 1976) were investigated for mutagenicity in the Salmonella/microsome assay (SAL-m), the Basc test on Drosophila (Basc), and the micronucleus test on mouse bone marrow (MN). Of the 31 chemicals tested, 15 were mutagenic in SAL-m. Five of these were also mutagenic in Basc and two in the MN test. Only one compound, pyrogallol, was active in all three test systems. None of the compounds positive in the two eukaryotic systems was inactive in the SAL-m assay, which underlines the sensitivity of the Ames test with regard to various mutagens. Of the compounds positive in the SAL-m test, seven would not have been recorded if only the generally used Vogel-Bonner medium had been used. Of these substances, two were mutagenic in one or the other of the two eukaryotic test systems. (62 Refs)

109. IN VITRO METABOLISM OF ACRYLONITRILE TO 2-CYANOETHYLENE OXIDE, REACTION WITH GLUTATHIONE, AND IRREVERSIBLE BINDING TO PROTEINS AND NUCLEIC ACIDS.

Guengerich FP, Geiger LE, Hogy LL, Wright PL
Dept. Biochemistry and Center in Environmental Toxicology, Vanderbilt Univ. Sch. Medicine, Nashville, TN, 37232
Cancer Res; 41(12):4925-4933 1981

The metabolism of the suspected carcinogen acrylonitrile was studied using subcellular fractions isolated from rats and humans. Irreversible binding of radioactive label from [1-14C]- or [2,3-14C]acrylonitrile to protein and DNA was enhanced by reduced nicotinamide adenine dinucleotide phosphate in the presence of rat liver microsomes or a reconstituted cytochrome P-450 system. During the reduced nicotinamide adenine dinucleotide phosphate-dependent reaction, HCN was produced, and the heme of cytochrome P-450 was destroyed. Rat brain microsomes did not produce detectable levels of metabolites. Conclusive evidence of metabolically mediated binding of acrylonitrile to protein and DNA in human systems was not found. With rats, metabolism was induced by pretreatment of animals with either phenobarbital or 5,6-benzoflavone. Labeled 2-cyanoethylene oxide was found to bind irreversibly to calf thymus DNA and microsomal protein. The extent of binding was greater in the case of 2,3-14C-labeled than 1-14C-labeled material. The relative first-order rate of acrylonitrile binding to calf thymus DNA in rat liver microsomal systems was one to two orders of magnitude less than that for 1,1,2-trichloroethylene and three orders of magnitude less than that for vinyl chloride or vinyl bromide. Rat liver microsomes or a reconstituted cytochrome P-450 system catalyzed the mixed-function oxidation of acrylonitrile to 2-cyanoethylene oxide. 2-Cyanoethylene oxide has a half-life of about 2 hr in neutral buffer at 37 C. This epoxide was found to serve as a substrate for microsomal epoxide hydrolase. HCN was released during hydrolysis of 2-cyanoethylene oxide or reaction of the epoxide with reduced glutathione; however, HCN release in either case was not stoichiometric with epoxide disappearance. 2-Cyanoethylene oxide reacted less rapidly with reduced glutathione than did acrylonitrile. Rat liver cytosol preparations contained glutathione S-transferase activity towards acrylonitrile and greater activity with 2-cyanoethylene oxide as a substrate. Cytosol preparations from rat brain and human liver had no detectable glutathione S-transferase activity towards acrylonitrile but did exhibit some activity towards 2-cyanoethylene oxide. These studies establish the basic pathways involved in the metabolism of acrylonitrile and should provide a basis for examination of the relevance of these individual steps and their roles in bioactivation and detoxication under more physiological situations. (Author abstract) (40 Refs)

REVIEWS AND OTHER COMPOUNDS

110. PATTY'S INDUSTRIAL HYGIENE AND TOXICOLOGY. VOLUME 2A. TOXICOLOGY.

Clayton GD, Clayton FE
San Luis Rey, CA
Patty's Industrial Hygiene and Toxicology. Volume 2A. Toxicology. New York, John Wiley and Sons, 1467-2878 pp., 1981.

Toxicity and other data are presented for elements and compounds that are currently of primary interest to industry. Individual chapters describe the sources and production, uses and industrial exposures, physical and chemical properties, acute and chronic toxicity, carcinogenicity, and mutagenicity of 40 metals, organic sulfur compounds, epoxy compounds, esters, ethers, aromatic nitro and amino compounds, phenols and phenolic compounds, aldehydes and acetals, heterocyclic and miscellaneous nitrogen compounds, and phosphorus, selenium, and tellurium. Analytic procedures and recommended threshold limit values also are discussed. (4197 Refs)

111. THE TWO-GENERATION SACCHARIN BIOASSAYS (MEETING ABSTRACT).

Arnold DL
Health Protection Branch, Ottawa, Canada
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Saccharin was discovered over 100 yr ago and the controversy regarding its safety for human consumption started shortly therafter and has not subsided appreciably in the intervening decades. The consumption of saccharin, particulary in North America, started to escalate when under new standards of identity, the US Food and Drug Administration allowed foods containing artificial sweeteners to be promoted as 'nonnutritive' or 'noncaloric' sweeteners for use by the general public. In 1969, when cyclamates were banned, at least 10 single generation feeding studies were undertaken to more accurately assess the toxicological consequences resulting from the anticipated increased consumption of saccharin. While none of these studies resulted in any overt regulatory action, the introduction of the two-generation chronic toxicity/carcinogenicity bioassay added a new total to the toxicologists' arsenal. Three studies have since been conducted using the protocol, and the results from these studies clearly show that when rats were exposed to diets containing 5 or 7.5% sodium saccharin from the time of conception to death, and increased frequency of urinary bladder cancers were predominately found in the males. While some study results suggested that impurities in commercial saccharin, or the presence of urinary tract calculi may have been responsible for the observed bladder tumors, it now appears that these possibilities are highly unlikely. The mechanisms by which saccharin elicited the bladder tumors using the two-generation experimental model has not been ascertained. (no Refs)

112. THE CURRENT USE OF STUDIES ON PROMOTERS AND COCARCINOGENS IN QUANTITATIVE RISK ASSESSMENT (MEETING ABSTRACT).

Stara JF
U.S. Environmental Protection Agency, Cincinnati, OH
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Under the Clean Water Act, the US Environmental Protection Agency is required to develop an approach for controlling the release of hazardous pollutants in water. As part of this effort, the Environmental Criteria and Assessment Office (ECAO) in Cincinnati, with the support of other groups in the Office of Health and Environmental Assessment (OHEA), was assigned the task of assessing the potential health risks associated with contamination of the aquatic environment. Initially, ECAO's major responsibility was to prepare the Human Health Effects Assessment Chapters of the 65 Ambient Water Quality Criteria Documents (AWQCDs) which were required under the Consent Decree of Environmental Defense Fund vs Train. Along with scientists from other Agency offices, academia, and private sector, ECAO developed guidelines for deriving ambient water quality criteria and applied these guidelines to the available data on the 129 compounds included in the 65 documents. Several of the pollutants covered in these documents have been shown to be promoters or cocarcinogens. For example, phenol appears to have tumor promoting activity in mice when repeatedly applied after initiation with either dimethylbenzanthracene (DMBA) or benzo(a)pyrene (BaP). Similarly, it has recently been reported that 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is a potent liver promoter and a cocarcinogen. However, it became apparent that satisfactory methods had not yet been developed for using promotion/cocarcinogenicity data in quantitative risk assessment. For this reason, the derived criteria for some pollutants with promotion/cocarcinogenic activities were based on carcinogenicity, toxicity, and organoleptic effects. (no Refs)

113. MUTAGENICITY OF OIL-SHALE ASH.

Whong WZ, Sorenson WG, Elliott JA, Stewart J, Simpson J, Piacitelli L, McCawley M, Ong T
Div. Respiratory Disease Studies, Natl. Inst. for Occupational Safety and Health, 944 Chestnut Ridge Road, Morgantown, WV, 26505
Mutat Res; 103(1):5-12 1982

Three oil shale samples were analyzed for mutagenicity in four test systems after extraction with solvents. In Salmonella typhimurium, extracts were highly mutagenic with Ames his reversion and ara-resistant systems; mutation induction was independent of metabolic activation and was of the frameshift type. The extracts showed substantial killing effect, but they failed to induce ad-3 reversion in Neurospora crassa, gene conversion and mitotic crossing-over in Saccharomyces cerevisiae, or TGr mutation in cultured CHO cells. (14 Refs)

114. INVESTIGATIONS ON RADIOSENSITIVE AND RADIORESISTANT POPULATIONS OF DROSOPHILA MELANOGASTER. XIII. EFFECTS OF RADIORESISTANT MUTANTS (RAR) ON CHEMICAL (EMS) MUTAGENESIS.

Nothel H, Strese B
Institut fur Genetik, Freie Universitat Berlin, Berlin-Dahlem, W. Germany
Mutat Res; 103(1):87-90 1982

After treatment with ethyl methanesulfonate (EMS), treated Drosophila melanogaster males were mass mated to Basc females and treated D melanogaster females to males carrying Ys In(1)EN car f In(1)dl49 v y-YL/0. Sex-linked recessive lethals were scored as percentage of X-chromosomes tested, after treatment of various germ-cell stages of +K (normals), ROI/0, rar-3, and ROI/40 with EMS in various forms of application (injection or fed). Mutation frequencies indicated normal efficiency of EMS injection. High mutational yields from mature oocytes indicated a reasonable uptake of EMS after feeding and confirmed the marked sensitivity of stage-14 oocytes compared with stage-7 and younger oocytes. The low sensitivity of immature oocytes to EMS makes comparison between genotypes somewhat difficult. The system of relative radioresistance, which has evolved under the irradiation conditions of the populations ROI and ROI/4, is not based on specific radiobiological processes but involves more general pathways of mutagenesis. (13 Refs)

115. MUTAGENESIS AND TRANSFORMATION OF C3H 10T 1/2 CELLS TREATED WITH ETHYL METHANESULFONATE.

Evans HH, Wilkins L, Horng MF, Santoro C, Evans TE, Glazier KG
Div. Radiation Biology, Dept. Radiology, Case Western Reserve Univ., Cleveland, OH, 44106
Mutat Res; 84(1):203-219 1981

The effects of ethyl methanesulfonate (EMS) on survival (plating efficiency: PE), mutagenesis (induction of ouabain resistance), and transformation (induction of altered colony morphology on monolayers or of colony formation in semisolid media) were studied. Cell lines used included mouse embryo-derived C3H 10T1/2 (clone 8), the chemically transformed counterpart MCA, BALB 3T3, and virally transformed SVT2. Cell monolayers were treated with various concentrations of EMS for 2 hr. Incubation of confluent monolayers for 4 hr following EMS exposure allowed some excision repair of DNA to occur and resulted in increased survival, transformation, and mutation. Extension of the repair period to 24 hr allowed further DNA repair to occur and resulted in lower rates of transformation and mutation than after 4-hr incubation. The PE of one ouabain-resistant (Oua-R) strain increased as the density of ouabain-sensitive (Oua-S) cells increased. In other Oua-R strains PE was reduced when Oua-S density increased over 1 x 10(3) cells/square cm. Results indicate that the length of DNA repair periods affects the frequencies of mutation and transformation. (61 Refs)

116. METHYL METHANE-SULPHONATE (MMS) INDUCED SCES ARE REDUCED BY THE BRDU USED TO VISUALISE THEM.

Ockey CH
Paterson Lab., Christie Hosp., Holt Radium Inst., Withington, Manchester M 209 BX, England
Chromosoma; 84(2):243-256 1981

SCE induction in synchronized CHO cells treated with methyl methane sulfonate (MMS) in G1 was studied over successive pairs of cell cycles by introducing bromodeoxyuridine (BrdU) at consecutive G1 stages. When individual cell cycle SCE values were calculated from the data, anomalous results were obtained with ratios of 1.0:1.8:2.1 for the first three cycles but a negative value for the fourth cycle. Further studies using different BrdU concentrations showed that MMS induced SCEs were reduced by values exceeding 50% in DNA containing high levels of incorporated BrdU. This reduction was dose dependent and accounted for the anomalous results obtained over successive cycles. Lesions leading to chromatid exchanges were also reduced by the same mechanism. SCEs induced by UV irradiation were also decreased but those induced by the cross-linking agent nitrogen mustard (HN2) remained unaffected. The results indicate that not only are SCE lesions induced by MMS, UV or HN2 expressed independently of the 'spontaneous' SCEs induced by BrdU but that SCE lesions are multiple in nature. Mechanisms by which SCE lesions could be repaired in BrdU containing DNA are discussed. SCE lesions in MMS treated cells arrested in G1 with arginine deprived medium (ADM) are repaired without the presence of BrdU in the DNA. An opposite effect is seen however in the control cells, where SCEs are increased with time spent in ADM arrest. These interactions between the effects of MMS, BrdU and ADM arrest are discussed. (Author abstract) (14 Refs)

117. FORMATION OF MACROMOLECULAR COMPLEXES AND OTHER EFFECTS OF DNA TREATMENT WITH DIETHYL AND DIMETHYL SULFATE: PHYSICOCHEMICAL AND ELECTRON MICROSCOPIC STUDIES.

Kubinski H, Kubinski ZO, Fiandt M, Konopa G
Univ. Wisconsin, 183 Medical Sciences Building, Madison, WI, 53706
Carcinogenesis; 2(10):981-990 1981

Production of macromolecular complexes by DNA exposed to diethylsulfate (diES) or dimethylsulfate (diMS) was investigated by a variety of techniques. A fraction of DNA treated briefly with diES or diMS moves during velocity centrifugation experiments less rapidly than most of the control, untreated DNA and more rapidly through gels during electrophoresis. This apparent decrease in size is paralleled by formation of large DNA aggregates with mobilities indicating mol wt several times that of control DNA. Basic protein in the mixture increases the rate of formation of such complexes. Alkylated DNA tends to bind to both biological and non-biological materials, as indicated by increased attachment of DNA to columns built with methyl-esterified serum albumin and in its quantitative retention on nitrocellulose filters. DNA exposed to diMS decreases its density in CsCl gradients. A mixture of two or more DNAs of different densities exposed to diMS produces a UV-absorbing band which is found in such gradients at an intermediate density. When the alkylation reaction is carried out in the presence of a protein, a portion of DNA bands at a density intermediate between that of the DNA and the protein, even in the presence of an ionic detergent. Electron microscopy of the alkylated DNA shows multiple single-strand breaks and peel-off whiskers of denatured DNA. Aggregates of DNA molecules become visible upon further incubation of DNA with the alkylating agent. It is suggested that the DNA-DNA and DNA-protein complexes play an important role in carcinogenesis and mutagenesis. (22 Refs)

118. CONVERSION OF CHLORINATED NITROBIPHENYL ETHERS AND THEIR DERIVATIVES TO MUTAGENS BY WHITE-SPOTTED CHAR, SALVELINUS LEUCOMAENIS, LIVER HOMOGENATE.

Miyauchi M, Takagi M
Lab. Food Hygiene, Faculty of Fisheries, Hokkaido Univ., Hakodate 041, Japan
Bull Jpn Soc Sci Fish; 47(2):243-250 1981

Mutations were induced by p-nitrobiphenyl ether, its chlorinated forms, and their nitroso derivatives in a Salmonella typhimurium assay without liver homogenate. Liver homogenate from the white-spotted char increased mutagenicity of the compounds slightly and greatly increased the mutagenicity of amino derivatives. (23 Refs)

119. A COMPARATIVE GENOTOXICITY STUDY OF CHLOROGENIC ACID (3-O-CAFFEOYLQUINIC ACID).

Stich HF, Rosin MP, Wu CH, Powrie WD
Environmental Carcinogenesis Unit, British Columbia Cancer Res. Centre, 601 West 10th Avenue, Vancouver, British Columbia V6T 1W5
Mutat Res; 90(3):201-212 1981

Genotoxicity of chlorogenic acid was evaluated in three different bioassays that depend on different tester cells and endpoints: reverse mutation in Salmonella typhimurium, gene conversion in Saccharomyces cerevisiae, and chromosome aberration in Chinese hamster ovary cells (CHO). No significant increase in mutagenesis in either Salmonella tester strain TA98 or TA100 was observed with or without addition of S9 mixture. A significant increase in his+ reversion frequency occurred when the strains were exposed to a mixture containing both Mn++ and chlorogenic acid. Addition of Cu++ was without effect. Neither transition metal induced his+ revertants alone. Caffeic acid produced a similar response pattern, but quinic acid was not mutagenic even in the presence of Mn++. Chlorogenic acid induced a greater than 2x increase in tryptophan (trp+) conversion frequency at non-toxic concentrations. Presence of S9 suppressed the response and transition metals enhanced it. Chlorogenic acid was also found to be a direct acting clastogen. In the presence of Mn++, chromatid breaks and exchanges were induced by chlorogenic acid at doses 10x lower than required by chlorogenic acid alone. (31 Refs)

120. ADVANCES IN THE METABOLIC ACTIVATION OF CARCINOGENS.

Ivanetich KM
Dept. Medical Biochemistry, Univ. Cape Town Medical Sch., Observatory, Cape Province, South Africa
S Afr Cancer Bull; 25(1/2):105-116 1981

Of the known chemical carcinogens, an ever-increasing number require metabolic activation to elicit their mutagenic and carcinogenic effects. In a review, it is noted that the enzymes known as cytochrome P-450 alone or in conjunction with other enzymes are involved in this activation. The activated metabolites may initiate carcinogenesis by covalently binding to selected sites on nuclear DNA in somatic cells. Detailed pathways are presented for a number of carcinogens, such as chlorinated ethylenes, aflatoxin B1, acetylaminofluorene and benzpyrene. (22 Refs)

121. CHEMICAL AND ENVIRONMENTAL AGENTS IN GASTROINTESTINAL CARCINOGENESIS.

Deschner EE, De Cosse JJ, Sherlock P
Lab. Digestive Tract Carcinogenesis, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Clin Gastroenterol; 10(3):755-771 1981

A review is presented of incidence, risk factors, and chemical and environmental agents involved in induction or promotion of cancer of the gastrointestinal system. Presence of ingested agents in foods and experimental and clinical evidence for cancer causation are discussed. Carcinogenesis is considered with respect to the esophagus (nitrosamines, mycotoxins, promotional factors), stomach (nitrites and polycyclic hydrocarbons, mycotoxins, agricultural products, polychlorinated biphenyls, experimental carcinogens), and large bowel (nitrites, aflatoxins, diet, carrageenan, chemical carcinogens, nitroso compounds, biphenyls, symmetrical 1,2-dialkylhydrazines and azoalkanes and azoxyalkanes). Chemicals with known gastric tumor induction capability in animals are tabulated from published reports. (74 Refs)

122. LUNG CANCER.

Woll JE

Univ. Rochester Sch. Medicine and Dentistry, Rochester, NY

Practical Cancer Chemotherapy. Rosenthal SN, and Bennett JM, ed. Garden City, NY, Medical Examination Publishing Co., 461 pp., 1981.

In America lung cancer accounts for 22% of all cancers in males, 8% in females. Median survival from diagnosis remains less than 6 mo, with an overall 5-yr-survival rate of 8%. Cigarette smoking, occupational exposure to lung irritants, and demographic variables all contribute to the etiology of lung cancer. A definite dose-response relationship exists between lung cancer risk and number of cigarettes smoked daily, with a 20-fold increase among those who smoke two or more packs a day. Lung malignancies can be produced in laboratory animals by application of tobacco tar and other carcinogens found in cigarette smoke. Occupational exposure to arsenic, asbestos, chromium, nickel, chloromethyl ethers, and radiat ion is also associated with an increased risk of lung cancer. The pathology, clinical features, diagnosis and evaluation, and treatment of the various lung malignancies including non-small cell and small cell lung cancer are reviewed. (44 Refs)

123. PROMOTION OF LUNG TUMORS IN MICE (MEETING ABSTRACT).

Witschi HP

Oak Ridge National Laboratory, Oak Ridge, TN

International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Experimental evidence obtained during the last 6 yr shows that several elements of two-stage carcinogenesis apply to the development of lung tumors in Strain A Swiss-Webster mice. At least three agents which have been identified as promoters in skin, urinary bladder, and liver will also enhance tumor formation in lung: phorbol, saccharin, and butylated hydroxytoluene (BHT). The antioxidant BHT acts in many respects like a typical promoting agent: it is effective if animals are treated after exposure to an initiating agent, but not if they are treated beforehand. Administration of BHT can be delayed up to 5 mo after urethan treatment and still enhance tumor formation. BHT enhances lung tumor formation regardless of its route of administration (ip injection, gavage, or ingestion in the diet). The lowest dose of BHT required to produce an effect has not yet been determined. In at least one mouse strain, BHT also enhances tumor formation in animals initiated with 3-methylcholanthrene or diethylnitrosamine. On the other hand, no evidence is available yet to show that BHT would enhance tumor development in animals treated with subcarcinogenic doses of an initiating compound. Nor has it been possible to produce more tumors with BHT in mouse strains which have a low spontaneous tumor incidence and respond poorly to urethan. The question has not been resolved whether BHT accelerates growth of preformed tumors only or whether it induces the formation of more tumors. (no Refs)

124. SURFACE ACTIVE AGENTS AS TUMOR PROMOTERS (MEETING ABSTRACT).

Boyland E

London School of Hygiene and Tropical Medicine, London, England

International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Initiation and promotion are different stages in carcinogenesis. Initiators are generally mutagenic and if a substance or procedure is carcinogenic and not mutagenic the effect is most probably tumor promotion. Many carcinogens are complete, having both initiating and promoting activity. Promoters alone induce tumors because initiators are present in the diet or the environment. Promoters can be physical as with trauma and foreign bodies such as with asbestos. Promoters are often organotropic; phenobar bitone, clofibrate and valium act on the liver of rodents. Of the 14 types of tumor promoters listed, the class of surfactants includes many different compounds. Saccharin, cyclamate and tryptophan act on the rat bladder, and lithocholic acid on the colon. The sweetening agents and bile acids reduce interfacial tension by some 20% in concentrations at which they are present in urine or feces when given in doses which promote tumors in rats. The incidence of cancer of esophagus and mouth is high in smokers who consume spirits rather than beer. The cigarette provides initiators and the alcohol acts as promoter. The alcohol present in spirits would reduce the interfacial tension appreciably in the mouth and esophagus so that the carcinogenic action of spirits is probably due to the promoting action of the alcohol because of its surface activity. With promoters of the surfactant type there are levels below which the effects are negligible and so there may be safe levels. This is clearly the concentration attained at any particular time rather than the total dose. The effect of the surface active tumor promoters is probably due to action on cell membranes. The mode of action of solvents such as chloroform and benzene is probably similar. There must be safe or threshold levels for the surface active and other promoters, but probably not for materials like asbestos which remain in the body. It is possible that there are no safe levels for initiators, but if there were they might vary with exposure to promoters. (no Refs)

125. ROLE OF NUTRITIONAL FACTORS IN REALIZATION OF BIOLOGICAL EFFECTS OF XENOBIOTICS.

Sharmanov TS

Kazakh Branch, Inst. Nutrition, Alma-Ata, USSR

Vopr Pitan; (5):51-57 1981

The role of nutritional factors in the metabolism of pesticides, nitrosamines, and aflatoxins is reviewed. Nitrites present in canned meat or fish can react with exogenous amines to yield carcinogenic nitroso compounds. Dietary deficiency of vitamin C and essential amino acids enhanced the carcinogenic activity of N-nitrosopiperidine in guinea pigs. Deficiency of the essential amino acids and retinol enhanced the incidence of aflatoxin B1-induced tumors in rats. (33 Refs) (In RUS)

126. MODEL FOR HUMAN CARCINOGENESIS: ACTION OF ENVIRONMENTAL AGENTS (MEETING ABSTRACT).

Moolgavkar SH
Institute for Cancer Research, Philadelphia, PA
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Current statistical prescriptions for low-dosage extrapolation of carcinogenic risk make no distinction between exposure to initiators and exposure to promoters despite the abundant data that these two classes of carcinogens have different modes of action. One reason for this is the lack of an appropriate model. In this paper, a model for carcinogenesis is presented which provides a framework for understanding the roles of 'spontaneous' events, hereditary factors, and environmental agents in human carcinogenesis and for interpreting experimental carcinogenesis. This model incorporates two features: (1) transition of target stem cells into cancer cells via an intermediate stage in two irreversible steps, (2) growth and differentiation of normal target and intermediate cells. Cast in mathematical terms the model can be fitted to age-specific incidence data on human cancers of both children and adults and can illuminate the relative importance of agents that affect transition rates, tissue growth and tissue differentiation. Within the context of the model, initiators act by affecting the transition rates, whereas promoters influence the kinetics of growth, especially of initiated cells. The model provides a good quantitative description of the epidemiology of carcinomas of the breast and of the lung. The data are consistent with the notion that hormones and cigarette smoke act as promoting agents in carcinoma of the breast and of the lung respectively. (no Refs)

127. AIR POLLUTION AND BIOLOGICAL DEFENCE.

Schlipkoter HW, Dolgner R
Med. Institut fur Umwelthygiene an der Univ., Gurlittstrasse 53, D-4000 Dusseldorf 1, W. Germany
Zentralbl Bakteriol [Orig A]; 172(4/5):299-311 1981

A review is presented of the effects of air pollution on defense mechanisms of the body which may in turn account for differences in individual reactivity to such pollution. Some important findings relating to this problem follow: deterioration of lung clearance after inhalation of NO2 and lead chloride; damage to alveolar macrophages by air-borne particulates in vitro and in vivo; enhanced activation of C3 complement fraction under the influence of air pollutants; higher frequency of enlarged tonsils and lymph nodes, of pathogenic bacteria on tonsillar surfaces, and of relatively lower lysozyme concentrations in children living in urban or industrialized areas; decreased resistance to infections related to inhalation of O3 or a lead aerosol; immuno-suppressive effect of heavy metals and organic compounds; allergic reactions to many chemicals; detoxification and toxification, eg formation of ultimate carcinogens, and of organic molecules; induction or inhibition of benzo(a)pyrene metabolism by particulate extracts or by CO, NO2, and lead; deficiency of DNA-repair in disease conditions predisposing to development of cancer; tendency, in allergic subjects, to a relatively lower incidence of cancer; adaptation to the effect of CO and SO2. These facts, and others not cited, support a close connection between various defense mechanism, air pollution, and its effects on the human organism. (55 Refs) (In GER)

128. PROPORTIONATE MORTALITY STUDY OF FUR DYERS (MEETING ABSTRACT).

Haring MK, Waxweiler RJ, Walrath J
National Institute for Occupational Safety and Health, Cincinnati, OH
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

In recent studies, numerous constituents of oxidative hair dyes were shown to be mutagenic by the Ames test; some were also proven to be carcinogenic, inducing tumors of the liver, lymphatic system or other sites, in laboratory animals. Epidemiologic studies have associated exposure to hair dyes with increased risks of breast, cervical and lung cancers and chromosomal damage among hairdressers and consumers. During the past century, fur dyers have used oxidative dyes extensively to tint and color animal fur. To investigate the health effects of long term exposures to oxidative dyes, a retrospective cohort mortality study is being conducted on 980 fur dyers and processors of the Fur, Leather and Machinists Workers Union who were pensioned between 1952 and 1977. The standardized mortality ratio (SMR), using age-sex-race, calendar time, and cause-specific mortality rates for United States, will be calculated for all causes of death including all malignant neoplasms. In addition to oxidative dyes, other possible occupational exposures are saw dust, used to absorb excess dye from furs, and formaldehyde. Analyses of job classifications and ethnic origins also will be conducted. (no Refs)

129. NUTRITION AND ENVIRONMENTAL HEALTH: THE INFLUENCE OF NUTRITIONAL STATUS ON POLLUTANT TOXICITY AND CARCINOGENICITY. VOLUME 2: MINERALS AND MACRONUTRIENTS.

Calabrese EJ
Environmental Health Program, Div. Public Health, Univ. Massachusetts, Amherst, MA
Nutrition and Environmental Health: The Influence of Nutritional Status on Pollutant Toxicity and Carcinogenicity. Volume 2: Minerals and Macronutrients. New York, John Wiley and Sons, 468 pp., 1981.

As part of a survey on the influence of nutritional status on pollutant toxicity and/or carcinogenicity, the roles of minerals (calcium, copper, iron, selenium, zinc, cobalt, iodine, magnesium, manganese, molybdenum, phosphorus, potassium, and sulfur), protein, fats, carbohydrates, specific amino acids, fiber, and synthetic antioxidants are detailed. A comprehensive, critical review of the literature and viable and socially relevant research hypotheses to be considered in the formulation of priority allocations are presented. Persons who may be at increased risk for development of adverse effects from pollutant exposures are indicated. (2115 Refs)

130. STUDY ON THE TRANSPLACENTAL AND POSTNATAL MODEL OF CARCINOGENESIS IN MICE (MEETING ABSTRACT).

Rossi L, Cabral JR, Della Prota JR
Division of Experimental Oncology A, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milano, Italy
Toxicologist; 1(1):154 1981

A study is reported on the cumulative carcinogenic effect of transplacental and postnatal administration of dimethylnitrosamine (DMN), urethane, ascorbic acid, cyclophosphamide, isoniazid, 3-(5-nitro-2-furyl)-imidazo (1,2-alpha)pyridine (NFIP) and rifampicin. DMN and urethane were administered in the drinking water to CTM outbred mice for periods covering pregnancy and/or lactation. The other compounds were given po or ip (cyclophosphamide) during pregnancy and lactation. A control group was available. The progeny of all treated animals was killed at 60 wk of age and the progeny of a further rifampicin-treated groups was killed at 90 wk of age. Under the present experimental conditions the group treated with isoniazid, rifampicin, ascorbic acid and cyclophosphamide showed no differences in tumor incidence when compared with controls. DMN, urethane and the nitrofuran NFIP induced multiple tumors at various sites. The present experiments indicate that DMN is not a transplacental carcinogen because a significant increase of tumors was observed only in the progeny exposed during the lactation period. Urethane was shown to be a transplacental carcinogen. Mice exposed to the nitrofuran NFIP during prenatal and postnatal period showed a clear carcinogenic response. The latter result is a further indication of the strong carcinogen effects of nitrofurans. The evidence here presented indicates that this biological model may prove useful for screening the potential carcinogenicity of chemicals. (no Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

DIETARY FACTORS IN CARCINOGENESIS

1. NUTRITION AND ENVIRONMENTAL HEALTH: THE INFLUENCE OF NUTRITIONAL STATUS ON POLLUTANT TOXICITY AND CARCINOGENICITY. VOLUME 2: MINERALS AND MACRONUTRIENTS.
Calabrese EJ
Environmental Health Program, Div. Public Health, Univ. Massachusetts, Amherst, MA
Nutrition and Environmental Health: The Influence of Nutritional Status on Pollutant Toxicity and Carcinogenicity. Volume 2: Minerals and Macronutrients. New York, John Wiley and Sons, 468 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

2. RETROSPECT AND PROSPECT OF STUDIES ON DIGESTIVE SYSTEM DISEASES IN CHINA.
Zhang X
Dept. Internal Medicine, Capital Hosp., Chinese Acad. Medical Sciences, Beijing, People's Republic of China
Zhonghua Xiaohua Zazhi; 1(1):1-4 1981
In CHI

3. EPIDEMIOLOGY OF PITUITARY ADENOMAS.
Gold EB
Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 Wolfe St., Baltimore, MD, 21205
Epidemiol Rev; 3:163-183 1981

4. BLADDER CANCER EPIDEMIOLOGY.
Matanoski GM, Elliott EA
Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 North Wolfe St., Baltimore, MD, 21205
Epidemiol Rev; 3:203-229 1981

5. THE EPIDEMIOLOGY OF BENIGN BREAST DISEASE.
Ernster VL
Dept. Epidemiology and International Health, 1699HSW, Univ. California, San Francisco, CA, 94143
Epidemiol Rev; 3:184-202 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

6. AIR POLLUTION AND BIOLOGICAL DEFENCE.
Schlipkoter HW, Dolgner R
Med. Institut fur Umwelthygiene an der Univ., Gurlittstrasse 53, D-4000 Dusseldorf 1, W. Germany
Zentralbl Bakteriol [Orig A]; 172(4/5):299-311 1981
In GER

7. CANCER AND THE PHYSICOCHEMICAL QUALITY OF DRINKING WATER IN QUEBEC.
Thouez JP, Beauchamp Y, Simard A
Dept. Geography, Univ. Montreal, Montreal, Quebec, Canada
Soc Sci Med [Med Geogr]; 15(1):213-223 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

8. ONCOGENIC VIRUSES.
Wyke JA
Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England
J Pathol; 135(1):39-85 1981

9. ROLE OF VIRUSES IN THE ETIOLOGY OF NATURALLY OCCURRING FELINE LEUKEMIA.
Essex M, Grant CK, Cotter SM, Hardy Jr WD
Dept. Microbiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115
Haematol Blood Transfus; 26:483-487 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

10. MAMMALIAN IN VIVO AND IN VITRO CYTOGENETIC ASAYS: A REPORT OF THE U.S. EPA'S GENE-TOX PROGRAM.
Preston RJ, Au W, Bender MA, Brewen JG, Carrano AV, Heddle JA, McFee AF, Wolff S, Wassom JS
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Mutat Res; 87(2):143-188 1981

11. BACTERIAL SYSTEMS FOR CARCINOGENICITY TESTING.
Mohn GR
Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands
Mutat Res; 87(2):191-210 1981

12. MUTAGENESIS BY CHEMICAL AGENTS IN V79 CHINESE HAMSTER CELLS: A REVIEW AND ANALYSIS OF THE LITERATURE.
Bradley MO, Bhuyan B, Francis MC, Langenbach R, Peterson A, Huberman E
Merck Inst. for Therapeutic Res., West Point, PA, 19486
Mutat Res; 87(2):81-142 1981

OTHER REVIEWS IN CARCINOGENESIS

13. CANCER BIOLOGY.
Ruddon RW
Biological Markers Program, NCI-Frederick Cancer Res. Center, Frederick, MD
Cancer Biology. New York, Oxford University Press, 344 pp., 1981.

14. AVOIDABLE CANCER: ATTRIBUTION OF RISK.
Doll R
Radcliffe Infirmary, Oxford, England
S Afr Cancer Bull; 25(3):125-146 1981

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CHEMICAL CARCINOGENESIS

Miscellaneous Agents

SERIES CK13 No. 82/05

MAY, 1982

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HYDRAZINES AND RELATED COMPOUNDS

1. THE IMMUNE RESPONSE TO CARCINOMA OF THE COLON IN A RAT MODEL: A TEMPORAL STUDY.

House AK
Queen Elizabeth II Medical Center, Nedlands 6009, Western Australia
Aust NZ J Surg; 51(5):487-493 1981

Carcinoma of the colon was induced in rats by treatment with 1,2-dimethylhydrazine (DMH). Macroscopic tumors were observed from 8 wk after commencing DMH injections and rapidly increased in mass to cause death of the animals between 20 and 27 wk later. Tumor immunity was assessed by the gross parameters of body, spleen and mesenteric lymph

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node weight and by in vitro tests of lymphocyte antitumor cytotoxicity and leukocyte migration inhibition by tumor and normal colon homogenates. Immune responses were recorded in control (saline treated) and in tumor (DMH treated) rats. Body wt of the tumor rats paralleled that of control animals until tumors were well advanced. At this time tumor animal body wt was significantly less than that of control animals. Spleen wt and in vitro lymphocyte antitumor cytotoxicity were significantly greater in tumor than in control rats and were so found soon after macroscopic tumors were observed. Mesenteric lymph node wt and leukocyte migration inhibition did not change until late in tumor development, but at this time there was an immune response in tumor animals. The study showed that carcinoma of the colon induced in rats was associated with an antitumor immune response and that this change occurred soon after macroscopic tumors were present. In spite of this the animals died of their neoplasms. (Author abstract) (27 Refs)

HETEROCYCLIC COMPOUNDS

2. METABOLIC ACTIVATION OF A TRYPTOPHAN PYROLYSIS PRODUCT, 3-AMINO-1-METHYL-5H-PYRIDO(4,3-B)INDOLE (TRP-P-2) BY ISOLATED RAT LIVER NUCLEI.

Mita S, Yamazoe Y, Kamataki T, Kato R
Dept. Pharmacology, Sch. Medicine, Keio Univ., Shinanomachi, Shinjuku-ku, Tokyo 160, Japan
Cancer Lett; 14(3):261-266 1981

The abilities of nuclei and microsomes to convert 3-amino-1-methyl-5H-pyrido[3,4-b]indole (Trp-P-2) to an active mutagen were compared. Nuclei from polychlorinated biphenyl or methylcholanthrene-treated rats activated Trp-P-2 and caused a greater number of revertants in the Salmonella mutation test than nuclei isolated from phenobarbitol-treated or non-treated rats. Similar pretreatment effects were observed with microsomal activation. (17 Refs)

3. MICROSOMAL NITROREDUCTASE ACTIVITY OF RABBIT KIDNEY AND BLADDER: IMPLICATIONS IN 5-NITROFURAN-INDUCED TOXICITY.

Zenser TV, Mattammal MB, Palmier MO, Davis BB
Geriatric Res., Education and Clinical Center (111G JB), Veterans Admin. Medical Center, St. Louis, MO, 63125
J Pharmacol Exp Ther; 219(3):735-740 1981

The reductive microsomal metabolism of N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide and p-nitrobenzoic acid was studied in different areas of the rabbit kidney. In view of the relatively low oxygen tension in the renal inner medulla and bladder mucosa, the results suggest that medullary and transitional epithelial nitroreductases may be involved in the pathogenesis of 5-nitrofuran toxicity. (50 Refs)

4. MUTAGENICITY AND CYTOTOXICITY OF ETHYLENE OXIDE IN THE CHO/HGPRT SYSTEM.

Tan EL, Cumming RB, Hsie AW
Biology Div., Oak Ridge Natl. Lab., P.O. Box Y, Oak Ridge, TN, 37830
Environ Mutagen; 3(6):683-686 1981

Cytotoxicity and mutagenicity of ethylene oxide (EO) in the Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl transferase (CHO/HGPRT) system were examined. EO was found to be a direct acting mutagen and cytotoxic agent. Mutation frequency showed a linear dose response; mutagenic activity of EO was 24.7 x 10(-6) mutants/clonable cell/millimole. Compared to halogenated ethanes such as ethylene dibromide, ethylene chlorobromide, and ethylene dichloride, EO is only less mutagenic than ethylene dibromide. S9 increased the cytotoxicity of ethylene chlorobromide and ethylene 5-25x and mutagenicity 4x; cytotoxicity of ethylene dibromide remained unchanged. (20 Refs)

5. ETHYLENE OXIDE (ETO): EVIDENCE OF CARCINOGENICITY.

Coene RF
National Inst. for Occupational Safety and Health, Cincinnati, OH
Vet Hum Toxicol; 23(6):439-443 1981

The potential of ethylene oxide (EtO) as an occupational carcinogen is discussed. Production, use, potential for occupational exposure, evidence of carcinogenicity in experimental animals, mutagenic and reproductive effects, epidemiologic evidence of cancer in humans, exposure standards, and guides are reviewed. Results in sub-mammalian test systems (Salmonella typhimurium, Escherichia coli, Neurospora crassa, Tradescantia paludosa, and Drosophila melanogaster) have indicated mutagenic properties of EtO. EtO has caused statistically significant increases in mononuclear cell leukemia in female Fisher 344 rats. Among male Fisher 344 rats, EtO induced peritoneal mesothelioma originating in the testicular mesothelium. Investigation of possible adverse effects (analysis of chromosomal aberrations in lymphocytes for all exposed workers and sperm analysis for the men) has shown higher incidence of aberration and sister chromatid exchange among workers exposed to EtO. Cases of peripheral neuropathy among exposed workers have been reported. The present standard (1-10 ppm as 8 hr time-weighted av) may need to be reexamined; its adoption preceded recognition of the carcinogenic potential of EtO and was intended only to protect against acute and nonmalignant chronic effects. (no Refs)

6. COMPARISON OF THE GENETIC ACTIVITY OF AF-2 AND NITROFURANTOIN IN LOG AND STATIONARY PHASE CELLS OF SACCHAROMYCES CERVISIAE.

Callen DF
Cytogenetics Unit, Queen Elibeth Hosp., Woodville, 5011, Australia
Environ Mutagen; 3(6):651-658 1981

The genetic and toxic effects of 2-(2-furyl)-3-(5-nitro-2-furyl)acrylic acid amide (AF-2) and nitrofurantoin (NF) in fungi were studied and compared to previous results in bacteria. When stationary phase Saccharomyces cerevisiae D7 cells were treated with NF up to 4.2 milliM, no decrease in cell survival or increase in conversion frequency was observed. Cells from log phase cultures, however, were sensitive to NF, and increasing concentrations of NF caused decreased cell survival and increased frequency of trp5 convertants. When D7 cells from both stages of growth were treated with increasing concentrations of AF-2, survival decreased; log phase cells were more sensitive. Although log phase cells responded to a much lower concentration of AF-2 than did stationary cells, frequency of gene conversion at the trp5 locus, ade2 mitotic recombination, and frequency of total genetically altered colonies at this locus in log phase cells were similar to those attained in stationary phase cells. AF-2 induced reversion at the ilv1 locus in stationary phase cells. Log phase cells were found to have a nitroreductase activity 5-6x higher than in stationary phase cells. (15 Refs)

7. DOSE RESPONSES OF FIVE HEPATOCARCINOGENS FOR THE INITIATION OF RAT HEPATOCARCINOGENESIS.

Imaida K, Shirai T, Tatematsu M, Takano T, Ito N

First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan

Cancer Lett; 14(3):279-283 1981

Dose response curves were generated for hepatocarcinogenesis in male Fischer 344 rats initiated by diethylnitrosamine (DEN), aflatoxin-B1 (AFB), N-2-fluorenylacetamide (FAA), 3'-methyl-4-dimethylaminobenzene (DAB), or dimethylnitrosamine (DMN). Two wk after initiation, animals were placed on a 0.02% FAA diet for 2 wk. Animals were partially hepatectomized (PH) at the end of wk 3 and killed at the end of wk 4. All five hepatocarcinogens exhibited clear dose response curves for initiation of hepatocarcinogenesis; both numbers and areas of hyperplastic nodules increased with increasing doses in all cases. AFB was the most potent initiator, and was effective at a dose as low as 0.25 mg/kg body wt. Sizes of nodules induced by DEN, FAA, and DMN were smaller than those induced by AFB and DAB. (12 Refs)

8. UPTAKE AND MUTAGENICITY OF AF-2 IN CHINESE HAMSTER V-79 SPHEROIDS UNDER AEROBIC AND HYPOXIC CONDITIONS.

Olive PL, Durand RE

Sect. Radiobiology, Johns Hopkins Oncology Center, 600 North Wolfe St., Baltimore, MD, 21205

Environ Mutagen; 3(6):659-670 1981

The effects of furylfuramide (AF-2) on Chinese hamster V-79 spheroids were investigated. V-79 spheroids were examined for mutation frequency (resistance to 6-thioguanine). Equitoxic AF-2 exposures indicated that spheroid cells were inactivated by approx 10x lower concentrations when exposure occurred under hypoxic conditions. Although cells showed an increased fluorescence after exposure to AF-2 under hypoxic conditions, fewer mutations were induced with hypoxia than with air. With hypoxia, all of the cells appeared equally fluorescent (demonstrating equal absorption of AF-2), except for the external layer of larger spheroid cells which appeared less fluorescent. Although no significant change occurred in diameter, cellularity, or sedimentation profiles of spheroids following AF-2 treatment, a decrease in vol was apparent in cells treated with AF-2 under hypoxia. Furthermore, the diameter of colonies measured 8 days after AF-2 treatment was reduced. When mutagenicity of AF-2 was determined using the entire spheroid population, the contribution of the internal subpopulation appeared to be masked by that of the rapidly dividing cells of the outer layer. (17 Refs)

INORGANIC AGENTS AND PARTICULATES INCLUDING FIBERS

9. MAXIMUM PERMISSIBLE CONCENTRATION OF CADMIUM OXIDE IN THE AIR OF RESIDENTIAL AREAS.

Kamkin AB
Res. Inst. Industrial Hygiene and Occupational Diseases, Sverdlovsk, USSR
Gig Sanit; (10):13-16 1981

Toxic, gonadotoxic, mutagenic, and embryotoxic effects of cadmium oxide (CO) were studied in random-bred albino rats. Inhalation exposure to CO at 0.1 mg/cubic meter caused CNS inhibition, decreased the contents of sulfhydryl groups in the blood and in the brain, increased the activity of alkaline phosphatase in the blood, increased the embryolethality, and increased the mutation rates of somatic and germ cells. It was recommended that the max permissible concentration of CO in the air of the residential areas should not exceed 0.005 mg/cubic meter. (3 Refs) (In RUS)

10. INDUCTION BY INORGANIC METAL SALTS OF SISTER CHROMATID EXCHANGES AND CHROMOSOME ABERRATIONS IN HUMAN AND SYRIAN HAMSTER CELL STRAINS.

Larramendy ML, Popescu NC, DiPaolo JA
Lab. Biology, NCI, Bethesda, MD, 20205
Environ Mutagen; 3(6):597-606 1981

The frequency of sister chromatid exchange (SCE) and chromosomal aberrations (CAb) induced by several inorganic salts previously tested for transformation in Syrian hamster cells (HEC) was examined. Nontoxic concentrations of inorganic metal salts (sodium arsenite, beryllium sulfate, and nickel sulfate) that caused transformation in HEC increased SCE and CAb in human lymphocytes and HEC. Induced SCE frequencies were similar in the two cell types; increases were dose-related. Compared to control values of 5-18 and 7-20 SCE/cell in human and HEC cells, respectively, metals induced an SCE range of 10-35/cell. Sodium arsenite was most effective in human purified lymphocyte cultures, elevating SCE frequencies from 11.30 +-0.60 to 19.2 +-0.84 and 20.60 +-1.32 at 0.1 and 0.25 ug/ml, respectively. Sodium arsenate, beryllium sulfate, and nickel sulfate similarly increased SCE frequency but at 100x higher concentrations. Sodium arsenite and sodium arsenate, but not sodium tungstate, increased SCE frequency in whole human blood cultures. All tested inorganic metals except sodium tungstate induced SCE in HEC to approx 8x control values. CAb induction paralleled SCE induction, with chromatid aberrations being most frequent. (48 Refs)

11. MUTAGENICITY OF AIRBORNE PARTICLES FROM A NONINDUSTRIAL TOWN.

Whong WZ, Stewart J, McCawley M, Major P, Merchant JA, Ong TM
Div. Respiratory Diseases, Natl. Inst. Occupational Safety and Health, 944 Chestnut Ridge Road, Morgantown, WV, 26505
Environ Mutagen; 3(6):617-626 1981

The mutagenicity of air particles from a nonindustrial university town was examined. Air samples were collected during June-December, 1980. Dichloromethane extracts of all samples exhibited mutagenic activity in Salmonella typhimurium TA98, but secondary ethyl acetate/methanol extracts did not. No mutagenic activity was observed in extracts of blank filters. The number of revertants ranged from 34-355/mg particles and from 35-455/10 cubic meters of air. Mutagenic activity of samples collected in June and July did not require S-9 activation, while the mutagenicity of samples collected in October, November, and December was enhanced by S-9 activation. Dichloromethane extracts were also mutagenic using the arabinose-resistant assay system; such mutagenicity was dose-dependent and could be detected at a sensitivity of 1 cubic meter air/plate. Mutagenic activity in TA98 was found in acidic and polynuclear aromatic fractions but not in neutral or basic fractions. Samples of coal fly ash from a university power plant extracted with dichloromethane were mutagenic. (21 Refs)

12. AIR POLLUTION BY ASBESTOS AND OTHER FIBROUS DUSTS: A REVIEW OF THE WHOLE PROBLEM.

Lohrer W
Umweltbundesamt, Bismarckplatz 1, D-1000 Berlin, W. Germany
Staub; 41(10):387-395 1981

Air pollution problems caused by asbestos dust and other fibrous dusts are reviewed. Asbestos dust has been linked to as many as 2/3 cases of mesothelioma as well as to carcinoma of the lung. Asbestos fibers are universally present in the atmosphere in concentrations of 0.03-2,000 fibers/liter of air. The highest concentrations are found where asbestos-containing products are used in dust-producing situations, such as cutting, abrasion, transporting, weathering, and even disposal. No safe level of exposure has been found. Common sources of asbestos dust include asbestos cement used in building construction, drum brake linings, and artificial flooring. The carcinogenic effect of asbestos is related to the physical, rather than chemical, characteristics of the dust. Carcinogenicity begins with fiber length of over 2 microns (um) and diameter of under 1 um. Some artificial fibers, such as various forms of glass fibers, have similar carcinogenic properties. The principle method of reducing cancer risk due to asbestos is the substitution of other materials for asbestos. Such substitution requires overcoming serious economic problems. (32 Refs) (In GER)

AMIDES, CARBAMATES AND UREAS

13. SUSCEPTIBILITY OF VARIOUS STRAINS OF MICE TO URETHAN-INDUCED LUNG TUMORS AND DEPRESSED NATURAL KILLER CELL ACTIVITY.

Gorelik E, Herberman RB
Lab. Immunodiagnosis, Div. Cancer Biology and Diagnosis, NCI, NIH, Public Health Service, Bethesda, MD, 20205
JNCI; 67(6):1317-1322 1981

Inbred A/J, CBA/J, and C57BL/6 mice at age 7-8 wk were inoculated with 1 mg urethan/g body wt. Three mo later, 13.2, 1.8, and 0.1 tumors per lung were found in these mice, respectively. Cytotoxicity by spleen cells of normal and urethan-treated mice was analyzed in a 4-hr 51Cr release assay against YAC-1 cells. During the first 2 wk after treatment, urethan strongly suppressed the cytotoxicity by spleen cells of A/J mice but had relatively little effect on the reactivity of spleen cells of CBA/J mice. Natural killer (NK) activity was not suppressed in urethan-treated C57BL/6 mice. The effect of urethan on natural *in vivo antitumor resistance in the lungs* was studied by measurement of elimination from the lungs of [125I]deoxyuridine-labeled YAC-1 cells. Urethan caused profound and sustained suppression of in vivo NK reactivity in the lungs of A/J mice, had only a transient effect on CBA/J mice, and had no detectable effect on C57BL/6 mice. The differences in the effects of urethan on the natural antitumor resistance in the three strains of mice could not be attributed to a generally greater susceptibility of A/J mice to inhibition of NK activity, since cyclophosphamide (0.15 mg/g) equally suppressed the clearance from the lungs of the radiolabeled tumor cells in A/J, CBA/J, and C57BL/6 mice. These results indicate a positive correlation between susceptibility of A/J, CBA/J, and C57BL/6 mice to urethan-induced lung carcinogenesis and inhibition of in vitro and in vivo natural cell-mediated cytotoxicities and support the hypothesis that NK cells play a role in resistance to urethan-induced lung carcinogenesis. (Author abstract) (24 Refs)

14. ENHANCEMENT OF HEPATOCARCINOGENESIS BY SEQUENTIAL ADMINISTRATION OF CHEMICALS: SUMMATION VERSUS PROMOTION EFFECTS.

Williams GM, Katayama S, Ohmori T
American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Carcinogenesis; 2(11):1111-1117 1981

A comparative study was made of the sequential administration of the liver carcinogen, diethylnitrosamine (DEN), or the liver tumor promoter, phenobarbital, given after the liver carcinogen, N-2-fluorenylacetamide (FAA). The effects of the second carcinogen on preneoplastic cellular lesions induced by the first carcinogen were comparable to the effects of the promoter. In addition, both sequential exposures enhanced the ultimate carcinogenic effect, although the combination of FAA followed by DEN resulted in a greater number of malignant neoplasms. Thus, enhancement of carcinogenesis by a second chemical cannot be used by itself as evidence of a promoting action. Approaches to the more precise definition of promoters include exclusion of genotoxicity, identification of epigenetic mechanisms and lack of a summation effect with administration prior to genotoxic carcinogens. (Author abstract) (50 Refs)

15. EFFECT OF NEONATAL CASTRATION ON LIVER TUMOR INDUCTION BY N-2-FLUORENYLACETAMIDE IN SUCKLING BALB/C MICE.

Toh YC
Dept. Physiology, Univ. New England, Armidale, New South Wales 2351, Australia
Carcinogenesis; 2(11):1219-1221 1981

BALB/c mice were castrated at 2 days of age and control animals were sham-operated. Untreated male and female mice were also included for comparison. One-half of the mice in each group were fed on alternate days with 1.5% N-2-fluorenylacetamide suspended in 1% gelatine by stomach tube beginning 1 wk of age for a total of 14 feedings. The experiment was terminated when the mice reached 1 yr old. Approx 30% of the male mice, but none of the females, developed liver tumors in groups fed carcinogen. This male predominance in the incidence of hepatocellular carcinomas was completely abolished when the animals were castrated neonatally. No lesions were observed in the liver of mice treated with gelatine suspension alone except one with neoplastic nodule. Although it has been observed that liver tumors are produced more readily in younger than in older mice, the present investigation shows that male hormonal environment during early life is more important than the age on the development of liver tumors initiated by carcinogen. (Author abstract) (21 Refs)

AMINO ACID ANALOGS AND MODIFIED NUCLEIC ACID CONSTITUENTS

16. MUTAGENIC AND LETHAL EFFECTS OF [5-125I]IODO-2'-DEOXYURIDINE INCORPORATED INTO DNA OF MAMMALIAN CELLS, AND THEIR RBES.

Miyazaki N, Fujiwara

(c/o Fujiwara) Dept. Radiation Biophysics, Kobe Univ. Sch. Medicine, Kusunoki-cho 7-5-1, Chuo-ku, Kobe 650, Japan

Radiat Res; 88(3):456-465 1981

The mutagenic and lethal efficiencies of 125I decay, unifilarly incorporated as 5-iodo-2'-deoxyuridine (IdURD) into DNA [(125I)IdU/dT-DNA] of V79 Chinese hamster cells are described. The results are compared with those after exposure to the reference x-rays under frozen conditions, which minimize indirect and cellular metabolic effects such as DNA repair, age-response difference due to cycle traverse, and isotope dilution by cell division. The lethal and mutagenic effect of external x-rays in frozen state and at room temperature are compared. Unifilar IdU/dT cells were sensitized to x-ray killing 2x greater than at room temperature and 1.5x greater than at-79 C as normal (dT/dT) cells based on mean lethal dose. The rate of 6-thioguanine-resistance (6TGr) induction/rad was 6x greater than in IdU/dT cells than in the dT/dT cells after external x-irradiation at room temperature, and only 1.7x greater than at-79 C. Thus IdU/dT cells were more sensitized to x-ray killing and mutation. Indirect effects also played a role in these biological endpoints. The freezing effect on x-ray lethality was larger in IdU/dT cells than in dT/dT cells: mean lethal dose-reduction factors were 7.77 and 5.14, respectively. This difference suggests that x-ray-induced Auger phenomenon in iodine incorporated into DNA might enhance lethality in addition to a contribution of ordinal radicals. The efficiency and relative biological effectiveness (RBE) of cell inactivation and mutagenesis was examined. (34 Refs)

ALIPHATIC HALOGEN COMPOUNDS

17. SEQUENTIAL HISTOCHEMICAL CHANGES IN THE DISTRIBUTION OF ALKALINE PHOSPHATASE IN THE HEXACHLOROCYCLOHEXANE (HCCH) INDUCED LIVER TUMOURS IN PURE INBRED SWISS MICE.

Bhatt DK, Nigam SK, Lakkad BC, Babu KA, Karnik AB, Thakore KN, Kashyap SK

Natl. Inst. Occupational Health, Meghani Nagar, Ahmedabad 380 016, India

Cell Mol Biol; 27(2/3):231-238 1981

Inbred Swiss mice were given 500 ppm of technical grade hexachlorocyclohexane (HCCH) in the diet for 2, 4 and 6 mo. Their livers were investigated histochemically for alkaline phosphatase activity. After two mo of exposure the alkaline phosphatase activity has increased on the bile canaliculi and on the plasma membrane. The neoplastic nodules, after 4 mo exposure, have revealed very strong alkaline phosphatase activity, compared to normal areas. The activity remained intense in the tumor even after 6 mo feeding of HCCH; the activity at the plasma membrane level has disappeared in normal part of the tumor-bearing liver. The functional significance of alkaline phosphatase distribution at different locales has been discussed. (Author abstract) (32 Refs)

18. THE MORTALITY EXPERIENCE OF ARMY WORLD WAR II CHEMICAL PROCESSING COMPANIES.

Norman JE, Robinette CD, Fraumeni JF

Medical Follow-up Agency, Natl. Res. Council, 2101 Constitution Ave., Washington, DC, 20418

JOM; 23(12):818-822 1981

Tetrachloroethane was used by the Army during World War II in the impregnation of clothing for protection against mustard gas. Thirty-nine chemical processing companies were formed: 10 used tetrachloroethane as a solvent for the clothing impregnite and the remainder used a water solvent process. An age-specific analysis of mortality in relation to race, rank, and military occupational specialty (MOS) was performed in which observed numbers of deaths from principal cause groups were compared with those expected according to US standard mortality rates. Overall cancer mortality for 1,099 white males with tetrachloroethane exposure was 1.26 times that of 1,319 men not involved in the impregnation process. The risks for leukemia, lymphoma, and cancers of the genital organs were moderately elevated, but the numbers were small and no significant excesses were observed. (Author abstract) (17 Refs)

19. TOXIC DRUG EFFECTS ASSOCIATED WITH OXYGEN METABOLISM: REDOX CYCLING AND LIPID PEROXIDATION.

Kappus H, Sies H

Inst. Umwelthygiene, Univ. Dusseldorf, Moorenstrasse 5, D-4000 Dusseldorf, W. Germany

Experientia; 37(12):1233-1241 1981

Various endogenous and exogenous compounds exert cytotoxic effects via oxygen reduction. In general, these are reduced by intracellular enzymes (reductases of various kinds) in one-electron transfer reactions, before they in turn reduce O2 to O2-, the superoxide anion radical. Thus, a cycle is formed of O2 uptake at the expense of cellular reducing equivalents, notably NADPH, generating further active oxygen species. Structures capable of 'redox cycling' include catechols and other quinone compounds, iron chelates, and aromatic nitro compounds. Several anticancer agents, and also some mutagens, operate on this principle, and their toxic effects may be explained by redox cycling. The particular importance of hypoxic conditions for deleterious O2 effects is given by the concomitant flux through reductive as well as oxidative pathways. Toxic effects include membrane damage resulting from peroxidative reactions of polyunsaturated fatty acids (lipid peroxidation), as well as the attack of reactive oxygen species on proteins (enzymes) and nucleic acids; thus O2 metabolism is linked to carcinogenicity and mutagenicity. Lipid peroxidation is also induced by various halogenated compounds such as carbon tetrachloride. Again, hypoxic conditions are particularly critical because, on the one hand, metabolic activation leading to the free radical is enhanced and, on the other hand, oxygen required for the maintenance of lipid peroxidation is still available. Powerful antioxidant systems of the cell maintain low steady state concentrations of oxygen metabolites, and toxic effects may, in part, also be explained by the constant drain of reducing equivalents resulting from redox cycling. (Author abstract) (137 Refs)

POLYHALOGENATED RING COMPOUNDS INCLUDING INSECTICIDES

20. NEW PATHWAYS FOR CHLORINATED DIOXINS.

Hay A
Dept. Chemical Pathology, Univ. Leeds, Leeds, England
Nature; 294(5841):514-515 1981

Although 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is itself active, approx 1% of TCDD is metabolized. TCDD metabolism has been observed in vitro in Golden Syrian hamster hepatocytes. A reaction scheme for the metabolism of TCDD in rats and dogs is presented. Dynamic equilibrium between adipose and other tissues to maintain blood TCDD levels has been postulated for some animals. In humans, the TCDD blood levels are low but long-lasting. The metabolism of other polychlorinated compounds is discussed with reference to the Yusho I and II cases. Carcinogenic risk associated with TCDD is discussed. (no Refs)

21. MUTAGENICITY STUDIES ON FENTICONAZOLE, A NEW ANTIFUNGAL IMIDAZOLE DERIVATIVE.

Veronese M, Barzaghi D, Bertoncini A, Zadro M
Microbiology Section, Res. Div., Recordati S.p.A., Cas. Post. 10119, I-20100 Milano, Italy
Arzneim Forsch; 31(12):2142-2144 1981

The mutagenicity of alpha-(2,4-dichlorophenyl)-beta,N-imidazolylethyl 4-phenylthiobenzyl ether nitrate (fenticonazole) was tested in a forward mutational assay in Schizosaccharomyces pombe and a mitotic gene conversion assay in Saccharomyces cerevisiae. No mutagenicity was detected in either test. In vivo mammalian studies are in progress. (5 Refs)

22. THE SALMONELLA MUTAGENICITY ASSAY ON FENTICONAZOLE, A NEW ANTIFUNGAL IMIDAZOLE DERIVATIVE.

Veronese M, Barzaghi A, Bertoncini A, Zadro M
Microbiology Section, Res. Div., Recordati S.p.A., Cas. Post. 10119, I-20100 Milano, Italy
Arzneim Forsch; 31(12):2140-2142 1981

The antibacterial and antifungal imidazole derivative alpha-(2,4-dichlorophenyl)-beta,N-imidazolylethyl 4-phenylthiobenzyl ether nitrate (fenticonazole) was tested for mutagenicity in Salmonella typhimurium in the Ames test. No mutagenicity was detected in strains TA 1535, TA 1537, TA 1538, TA 98, or TA 100 with or without microsomal activation. (5 Refs)

DRUGS, COSMETICS, DETERGENTS AND OTHER COMMERCIAL MATERIALS

23. CAFFEINE INGESTION DURING PREGNANCY: IN UTERO EXPOSURE AND POSSIBLE EFFECTS.

Soyka LF
Clinical Pharmacology, Mead Johnson and Co., 2404 Pennsylvania Ave., Evansville, IN, 47721
Semin Perinatol; 5(4):305-309 1981

Mutagenic significance of caffeine in man and results of animal studies are reviewed. Topics include sources of caffeine exposure, absorption and distribution, mutagenicity, carcinogenicity, teratogenicity, influence on labor and delivery, aminophylline and lung maturation, and fetal breathing. Data on the caffeine content of beverages as consumed in the home, caffeine levels (term amniotic fluid, term cord blood, serum during therapy), and elimination of caffeine from serum of different population groups are summarized. Possible long-term hazards of caffeine exposure are listed. No convincing evidence exists for carcinogenicity of caffeine in animals. Teratologic effects of caffeine in more than 30 studies in animals were only found with high doses (250-800 mg/kg) toxic to the mother. In 10 studies using less than 50 mg/kg caffeine, congenital malformations were not increased. Both caffeine and theophylline have markedly prolonged and variable half-lives, especially in the premature infant; prolonged effects from these drugs cannot be dismissed. (29 Refs)

24. PHENOLS AND OTHER COMPONENTS OF OIL SHALE TARS AND ASBESTOS AS FACTORS MODIFYING THE CARCINOGENIC ACTION OF BENZO(A)PYRENE.

Bogovski P, Kung A, Winkmann F
Inst. Experimental and Clinical Medicine Hiiu Str. 42, 200016 Tallin, USSR
Arch Geschwulstforsch; 52(1):49-55 1982

The modifying action of phenols and other components (paraffins, olefins, naphthenes, aromatic hydrocarbons, neutral oxygen compounds) present in oil shale tar on the carcinogenic effects of benzo(a)pyrene (BP) and chrysotile asbestos dust was studied. Epicutaneous tests were performed on 500 C57Bl mice divided to 10 different treatment groups. The skin tumors found in this series included benign papillomas and malignant squamous epithelial carcinomas and basalomas. The tar fractions containing phenols and neutral oxygen compounds moderately potentiated the tumor-inducing action of BP, while the tar components alone induced at best papillomas. Another experimental series with 500 2.5-3-mo-old rats treated with BP, tar fractions and asbestos dust intratracheally revealed that the lung tumor incidence was highest after simultaneous administration of BP, asbestos dust and tar phenols. Asbestos dust potentiated the carcinogenic action of BP to the same extent as the tar phenols, whereas the latter had no such effect on the potency of asbestos dust. The lung tumors included epidermoid carcinomas, bronchial and alveolar adenocarcinomas and reticulosarcomas. (9 Refs) (In GER)

25. CIS-PLATINUM(II)DIAMMINODICHLORIDE-INDUCED MUTAGENESIS IN E. COLI K12: CROWDING DEPRESSION OF MUTAGENESIS.

Cunningham D, Pembroke JT, Stevens E
Dept. Microbiology, Univ. Coll., Galway, Ireland
Mutat Res; 84(2):273-282 1981

Repair-deficient Escherichia coli K12 strain AB1886 was more mutable by cis-platinum(II)diamminodichloride (cis-PDD) than repair-proficient strain AB1157. cis-PDD was not mutagenic in strains AB2463 recA and AB2494 lexA. Increasing plating density above 10(5) cells/plate did not give an equivalent increase in revertants/plate, demonstrating the existence of crowding depression of mutagenesis (CDM). CDM occurred to the same extent in excision-proficient and deficient strains, and growth rates were similar on plates of different cell densities, demonstrating that CDM is not due to mutation frequency decline or to inhibition of growth due to crowding or residual cis-PDD activity. Filtered plate wash from crowded plates, of either treated or untreated cultures, further reduced mutation frequencies over that due to CDM. (19 Refs)

26. EFFECT OF AQUEOUS FREE RADICALS AND CIS-DICHLORODIAMMINEPLATINUM (II) ON RADIATION-INDUCED BASE RELEASE FROM DNA.

Richmond RC, Kelman AD
Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Hanover, NH, 03755
Radiat Res; 88(3):476-488 1981

Free-radical contribution to thymine base residue release from purified Escherichia coli DNA irradiated in aqueous soln in the presence or absence of tert-butyl alcohol and cis-dichlorodiammineplatinum(II) (cis-DDP) was examined. Dependency of radiation-induced thymine residue release on the OH radical was standardized. It was demonstrated that the action of cis-DDP on thymine release operates frequently in ways other than an OH radical mechanism. (28 Refs)

27. METABOLIC ACTIVATION AND CYTOTOXICITY OF CYCLOPHOSPHAMIDE IN PRIMARY CULTURES OF POSTNATAL RAT HEPATOCYTES.

Acosta D, Mitchell DB
Dept. Pharmacology, Coll. Pharmacy, Univ. Texas at Austin, Austin, TX, 78712
Biochem Pharmacol; 30(23):3225-3230 1981

We have developed a model of primary cultures of postnatal rat hepatocytes to characterize the metabolic activation of xenobiotics to toxic intermediates and to study the mechanism(s) by which these chemicals produce cellular injury. This model was employed to investigate the cytochrome P-450 mediated biotransformation of cyclophosphamide (CP) to cytotoxic metabolites that nonspecifically alkylate DNA and cellular proteins. The parenchymal cells were isolated by an in situ collagenase perfusion technique and cultured for 24 hr prior to drug treatment. The cultures were then exposed to CP concentrations ranging from 1 x 10(-4) M to 1 x 10(-3) M for 24 hr. Initial studies indicated minimal toxicity to non-replicating parenchymal hepatocytes maintained in ornithine-supplemented, arginine-deficient medium. The addition of arginine permitted the overgrowth of fibroblasts in the same culture system. These fibroblasts then became the target of alkylating CP metabolites produced by the parenchymal cells. By day 3 after CP administration, cell number and total protein per dish decreased by over 40%. The morphology of the cultures changed dramatically because of fibroblast destruction. The cytotoxicity to dividing fibroblasts was eliminated by administering 2-diethylaminoethyl-2,2-diphenylvalerate hydrochloride (SKF 525-A), an inhibitor of the cytochrome P-450 monooxygenase system, to the co-cultures treated with CP. The alkylating metabolites of CP produced by parenchymal cells and released into the culture medium were quantitated by reacting aliquots of medium from CP-treated cells with 4-(p-nitrobenzyl)pyridine. These results provide both direct and indirect evidence of drug metabolism in cultured cells and suggest that this co-culture system can be utilized to evaluate the metabolic activation of xenobiotics. (Author abstract) (49 Refs)

28. FLOW CYTOMETRIC MEASUREMENT OF NUCLEAR DNA CONTENT VARIATIONS AS A POTENTIAL IN VIVO MUTAGENICITY TEST.

Otto FJ, Oldiges H, Gohde W, Jain VK
Fraunhofer-Institut fur Toxikologie und Aerosolforschung, D-5948 Schmallenberg-Grafschaft, W. Germany
Cytometry; 2(3):189-191 1981

Bone marrow samples from male NMRI mice administered cyclophosphamide (ip, 0.56-0.7 ml of 0.075-0.6% soln in physiological saline) were assayed for cellular DNA content. Staining was accomplished by addition of 9 ml disodium hydrogen phosphate containing 5 uM 4,6-diamidino-2-phenylindole, and fluorescence was measured by pulse cytophotometer. The coefficient of variation in the G1 peak of flow histograms increased during the first few days (especially 2-4 days) after injection. Both the magnitude and duration of the effect were dose-dependent through a range of 0-120 mg/kg. Reproducibility of results was high. (6 Refs)

29. MUTAGENIC ACTIVITY OF ISONIAZID AND ITS METABOLITES IN DIFFERENT TEST SYSTEMS.

Menon MM, Maru GB, Bhide SV
Carcinogenesis Div., Cancer Res. Inst., Bombay 400 012, India
Indian J Exp Biol; 19(10):939-942 1981

The mutagenic activity of isoniazid (INH) and its metabolites was examined using the Ames test system employing Salmonella typhimurium strains as well as two in vivo mammalian test systems (dominant lethal test and testicular DNA biosynthesis inhibition test). Possible prevention of mutagenic effects of INH using INH antitoxicants was also studied. INH without rat liver S9 mixture was mutagenic towards TA 100 and TA 1535. INH was not mutagenic to TA 92 or TA 98. Use of para-amino salicylic acid with INH significantly increased the number of revertants obtained. Two INH hydrazine metabolites, hydrazine sulfate (HS) and monoacetyl hydrazine (MAH), were mutagenic, HS for strains TA 92, TA 100, and TA 1535, and MAH for TA 100 and TA 1535. Negative results were obtained with diacetyl hydrazine and acetyl isoniazid. Of the three chemicals found to be positive, HS showed max mutagenicity in the presence of S9. Folic acid and pyridoxine slightly inhibited INH mutagenicity. The response of INH and HS was negative in the dominant lethal test. DNA synthesis in mouse testis was inhibited by INH, HS, MAH, and acetyl INH. It was concluded that the Ames test and the testicular DNA synthesis inhibition test show a good correlation in displaying mutagenicity of INH, HS, and MAH. (21 Refs)

30. INDUCTION OF EPSTEIN-BARR VIRUS EARLY ANTIGENS BY INTERCALATING CHEMICALS IN B95-8 CELLS.

Yamamoto N, Zur Hausen H
(c/o zur Hausen) Institut fur Virologie, Zentrum fur Hygiene der Universitat Freiburg, Hermann-Herder-Strasse 11, 7800 Freiburg, W. Germany
Virology; 115(2):390-394 1981

Various intercalating chemicals, such as ethidium bromide (ETB), proflavin (PF), acridine orange (AO), actinomycin D (AMD), methyl green (MG), Hoechst dye (HD), and trioxsalen (TX), have been tested for their effect on the induction of Epstein-Barr virus (EBV) antigens in several lymphoblastoid cell lines. ETB, PF, AO, and AMD enhanced induction of early antigens (EA) in B95-8 cells 3-to 10-fold. In contrast, viral capsid antigen (VCA) synthesis was not significantly affected by this treatment. Besides B95-8 cells only cells of the M-ABA line were induced to EA synthesis though to a lesser extent. All other cell lines tested did not respond to intercalating chemicals. Simultaneous treatment of B95-8 cells with ETB and 13-cis-retinoic acid inhibits the EA induction efficiently. ETB 'superinduced' EA neither in 12-O-tetradecanoyl-phorbol-12-acetate (TPA)- nor in iododeoxyuridine (IUdR)-treated B95-8 cells. (Author abstract) (29 Refs)

31. ENHANCEMENT OF S9 ACTIVATION BY S105 CYTOSOLIC FRACTION.

Forster R, Green MH, Priestley A

Water Res. Center, Henley Road, Medmenham, Marlow, Buckinghamshire, England

Carcinogenesis; 2(11):1081-1085 1981

The addition of supplementary cytosolic fraction greatly enhances the activation of 2-acetylaminofluorene (AAF) by uninduced 9,000 x g supernatant fraction (S9) in the Ames test. Uninduced S9 is poor at activating AAF in the Ames test (although it is effective in the liquid based fluctuation test) probably because cytosolic material diffuses into the bottom agar. An enhancing effect of cytosol supplementation was also observed with 2-aminoanthracene (AA) and 2-aminofluorene (AF) with uninduced S9. Using Aroclor-induced preparations, supplementation with cytosol enhanced the activation of benzo[a]pyrene and ethidium bromide. With AAF and Aroclor-induced preparations, supplementation with cytosol produces a slight but significant increase in activation, but interpretation is complicated by the fact that Aroclor 105,000 x g supernatant fraction (S105) alone efficiently activates AAF, AF and AA. Norharman potentiated the enhancing effect of Aroclor S105 on Aroclor-S9 activation of AAF but inhibited the activation of AAF by S105 fraction alone. The enhancing effect of S105 fraction may explain some, but not all, of the differences between liquid-based and agar overlay based activation. (Author abstract) (26 Refs)

REVIEWS AND OTHER COMPOUNDS

32. COMPARISON OF GROUNDWATER AND SURFACE WATER FOR PATTERNS AND LEVELS OF CONTAMINATION BY TOXIC SUBSTANCES.

Page GW

Dept. Urban Planning, Univ. Wisconsin, Milwaukee, WI, 53201

Environ Sci Technol; 15(12):1475-1481 1981

The assumption that groundwater (GW) is relatively uncontaminated with toxic substances (TS) in comparison with surface water (SW) was investigated. Sample data from over 1,000 wells and over 600 surface water sites in New Jersey were collected. Levels of TS were compared on the basis of max concentration, nonparametric av concentration and probability of detection. Analysis for 9 heavy metals, 27 light and 20 heavy chlorinated hydrocarbons showed 50 of these TS present in at least 5% of the samples. In terms of av detectable concentration, for 26 TS, there was no significant difference between GW and SW; 13 TS were higher in GW than SW, while 11 TS were higher in SW than GW. Apparently New Jersey GW is at least as contaminated with carcinogenic and TS as SW. Equal emphasis should be given to control of toxic substances in groundwater as is given to their control in surface water. (30 Refs)

33. SHORT-TERM TESTS FOR CARCINOGENS AND THEIR USES (MEETING ABSTRACT).

Garner RC
University of York, York Y01 5DD, England
Mutagenicity Testing, October 12, 1981, London, England Royal Society of Chemistry; 1981

Carcinogens can be divided into 5 major groups: (1) ionizing radiations; (2) viruses; (3) physical agents such as asbestos; (4) inorganic metal salts; and (5) organic chemicals. Group 5 constitutes the main class of substances giving rise to cancer. There are some 30 known organic chemicals or mixtures which can cause cancer in men, whereas some 2000 chemicals produce cancer in animals. If, as is the case, all known human carcinogens with the exception of arsenic can produce cancer in animals, it is likely that the reverse may also be true, namely that most animal carcinogens could produce cancer in humans. To test all the substances for which we have no biological data in animals would be an economic burden which could not be justified unless there were grounds for suspecting that chemical to be a hazard. To partially circumvent the problem of animal testing, a number of short-term tests for carcinogens have been devised. All rely on the unifying concept that organic chemical carcinogens are reactive chemical species (electrophiles) or must be metabolized to such. Chemical carcinogens will react with DNA, whether this be in bacteria or in mammalian cells, to cause an alteration in coding properties. In bacteria these reactions lead to mutations; in mammalian cells they lead to mutation and cancer. (no Refs)

34. OCCUPATIONALLY RELATED CARCINOGENESIS.

Waite DE
Dept. Family Medicine, Fee Hall, Michigan State Univ., East Lansing, MI, 48824
JAOA; 80(5):350-355 1981

The epidemiology of industrial carcinogenesis is discussed. The association between cancers of the urinary bladder and occupational exposure to workers in the German coal tar industry was first made in 1895 by Rehn. Cancer of the nose associated with chromate production was reported in 1890, and lung cancer from the same exposure in 1912. During the 1940s and 1950s the marked expansion of industry led to a significant increase in the number of observed relationships between occupational exposure and subsequent development of cancer. The Occupational Safety and Health Administration (OSHA), established in 1970, determines standards for exposure to carcinogens in industrial operations. OSHA currently exercises stringent controls over 19 specific chemicals which it labels as 'cancer specific agents.' Mechanisms of chemical carcinogenesis, primary carcinogens, and secondary carcinogens are also discussed. (42 Refs)

35. TOXIC HAZARDS RESEARCH UNIT: ANNUAL TECHNICAL REPORT JUN. 1979-MAY 1980.

MacEwen JD, Vernot EH
Dept. Community and Environmental Medicine, California Univ., Irvine, CA
Aerosp Med Biol; (223):149 1981

Chronic toxicity or oncogenic studies were carried out with methylcyclohexane, tricyclodecane, purified 1,1-dimethylhydrazine, and bicycloheptadiene. A subchronic inhalation study was conducted with shale derived JP-5 and DFM fuels. Acute toxicity studies were conducted on a variety of chemical agents used by the Air Force and Navy. (Author abstract) (no Refs)

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1. CHEMICAL CARCINOGENESIS.
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2. N-HEXANE AND ITS TOXICOLOGIC EFFECTS. A REVIEW.
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Scand J Work Environ Health; 7(3):157-168 1981

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Ioannides C, Delaforge M, Parke DV
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RADIATION CARCINOGENESIS

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DIETARY FACTORS IN CARCINOGENESIS

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Muller E, Rickenbach M
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U. S. Dept. Agriculture, Agricultural Res. Service, Fruit and Vegetable Chemistry Lab., Pasadena, CA, 91106
ACS Symp Ser; 170:43-59 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

8. ETIOLOGICAL CONCEPTS IN CERVICAL CARCINOGENESIS.
Kessler II
Dept. Epidemiology and Preventive Medicine, Univ. Maryland Sch. Medicine, 655 West Baltimore St., Baltimore, MD, 21201
Gynecol Oncol; 12(2,part2):S7-S24 1981

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11. GENETIC AND BIOCHEMICAL STUDIES WITH ATAXIA TELANGIECTASIA.
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Hum Genet; 59(1):1-9 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

12. THE HEALTH EFFECTS AND ECOLOGICAL SIGNIFICANCE OF CHLORINE RESIDUALS IN WATER.
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CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

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MODIFICATION OF CARCINOGENESIS

15. ROLE OF HORMONES INCLUDING DIETHYLSTILBESTROL (DES) IN THE PATHOGENESIS OF CERVICAL AND VAGINAL INTRAEPITHELIAL NEOPLASIA.
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Honn KV, Bockman RS, Marnett LJ
Dept. Biological Sciences, Wayne State Univ., Detroit, MI, 48202
Prostaglandins; 21(5):833-864 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

17. GENITAL CANCER AND VIRUSES.
Rapp F, Jenkins FJ
Dept. Microbiology, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
Gynecol Oncol; 12(2,part2):S25-S41 1981

18. VIRUS PAPILLOMAS IN HUMANS.
Nasemann T
Univ.-Hautklinik Eppendorf, Martinistr. 52, D-2000 Hamburg 20, W. Germany
Hautarzt; 32(11):601-606 1981
In GER

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CHEMICAL CARCINOGENESIS

Miscellaneous Agents

SERIES CK13 No. 82/06
JUNE, 1982

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HYDRAZINES AND RELATED COMPOUNDS

1. ABERRANT AND NONRANDOM METHYLATION OF CHROMOSOMAL DNA-BINDING PROTEINS OF COLONIC EPITHELIAL CELLS BY 1,2-DIMETHYLHYDRAZINE.

Boffa LC, Gruss RJ, Allfrey VG
Rockefeller Univ., New York, NY, 10021
Cancer Res; 42(2):382-388 1982

The alkylating carcinogen 1,2-dimethylhydrazine (DMH) induces colonic tumors with high incidence. The sites of in vivo modification of target macromolecules were studied using [methyl-3H]DMH Carcinogen binding to subcellular fractions of colonic epithelial cells was analyzed at time intervals ranging from 10 min to 36 hr, with particular emphasis on the alky-

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lation of nuclear constituents. DMH modifies not only nucleic acids but also histones and other DNA-binding proteins in the target cells. Separation of the 3H-methylated amino acids showed aberrant methylation patterns after exposure to [3H]DMH, as compared with methylations observed with [methyl-3H]methionine as a natural methyl group donor. DMH-modified histone H1 contained methylated lysine, arginine, and histidine residues not normally found, and other histones had abnormal methylarginine contents. High-mobility-group proteins and other nuclear proteins contained methyllysine residues not normally detected. Proteins known to be associated with template-active and more accessible DNA sequences, such as the high-mobility group proteins and the multiacetylated forms of histones H3 and H4, were preferentially damaged after exposure to [3H]DMH. The result suggests that carcinogen-induced chromosomal damage is not random and may selectively affect proteins in the actively transcribing or replicating genes in the target cells. That damage affects the amino acids most likely to be involved in DNA binding. (Author abstract) (47 Refs)

2. HISTOLOGICAL DISTRIBUTION OF COLON ADENOMA; OBSERVATION OF EXPERIMENTAL COLON ADENOMA AND HUMAN FAMILIAL COLON ADENOMA (MEETING ABSTRACT).

Nakamura S, Kino I
Dept. Pathology, Hamamatsu Univ., Sch. Medicine, Hamamatsu-shi, Shizuoka Pref. 431-31, Japan
Program and Proceedings of the 15th Meeting of the Japanese Research Society for Cancer of the Colon and Rectum held in Kagoshima, Japan, 24 July, 1981. The Japanese Research Society for Cancer of the Colon and Rectum, Osaka Pref. 589, Japan, 66 pp., 1981.

The histological distribution of colon adenoma induced by 1,2-dimethylhydrazine in ICR mice was examined with complete serial sections, and it was shown that the adenomas were located on the upper layer of the mucosa, and began with a single tubular adenoma showing endophytic growth. The cell dynamics was examined by the use of autoradiography with 3H-thymidine, and reversal of the growing zone and spread of adenoma over the superficial epithelium were not observed. Further, in four cases of human familial colon adenoma also it was seen that the adenoma began with a single tubular adenoma, and microlesions which could be called 'keim' of adenoma were present. The keim was composed of atypical epithelial cells, was located in the middle to upper part of the existing tubule, and was seen as a form of budding in the existing tubule to the lamina propria. These results indicate that these keims bud in the growing zone of the lower part of the tubule, move upward and grow with tubular epithelium, and become single tubular adenomas in the superficial layer of the mucosa. (no Refs) (In JPN)

3. EFFECTS OF DIETARY BRAN AND THE COLON CARCINOGEN 1,2-DIMETHYLHYDRAZINE ON A FECAL BETA-GLUCURONIDASE ACTIVITY IN MICE.

London JF, Clapp NK, Henke MA
Oak Ridge Graduate Sch. Biomedical Sciences, Univ. Tennessee, Oak Ridge, TN, 37830
Food Cosmet Toxicol; 19(6):707-711 1981

Daily variations in fecal beta-glucuronidase (BGLU) activity in BALB/c mice and variations in BGLU activity induced by different dietary brans and/or 1,2-dimethylhydrazine (DMH) were investigated. The effect of DMH on BGLU was significant. Three mo after DMH treatments, mice had persistently depressed BGLU activity compared to mice not treated with DMH. BGLU activities of animals on control or wheat bran diets were 4-5x higher than the activities in animals on either soya-bean bran or corn-bran diets and differed significantly from them. Animals fed the corn-bran diet consistently had the lowest BGLU activities in fecal stream. No synergistic action of any combination of variables was noted. (63 Refs)

4. GLUCOSE INCREASES EXPERIMENTALLY INDUCED COLORECTAL CANCER: A PRELIMINARY REPORT.

Ingram DM, Castleden WM
Univ. Dept. Surgery, Queen Elizabeth II Medical Center, Nedlands, Western Australia, 6009, Australia
Nutr Cancer; 2(3):150-152 1981

The possible role of dietary glucose in the development of 1,2 dimethyl-hydrazine (DMH)-induced experimental colon cancer in rats was studied. The addition of 1.6% glucose to drinking water resulted in significant increase in the number of DMH-induced large bowel tumors in rats, suggesting that a more detailed study should be made on the effect of glucose on the pathogenesis of human colorectal cancer. (11 Refs)

5. EXPERIMENTAL COLON CARCINOGENESIS IS FACILITATED BY ENDOGENOUS FACTORS IN THE INTESTINAL CONTENTS.

Lewin MR, Ferulano GP, Cruse JP, Clark CG
Dept. Surgery, Univ. Coll. London, Rayne Inst., University St., London, WC1E 6JJ, England
Carcinogenesis; 2(12):1363-1366 1981

The theory that endogenous factors in the intestinal contents may be pathogenic during large bowel carcinogenesis was tested in the dimethylhydrazine (DMH)-induced rat colon cancer model. Thirty female Wistar rats, each serving as their own control, had a surgical transection of the proximal colon with reanastomosis to the rectum, therby excluding part of the colon from fecal contact. All rats then received a course of DMH (40 mg/kg body wt/wk sc for 10 weeks) while fed on Vivonex. This diet was selected because it lacks known exogenous (dietary) cocarcinogens. It also produces mucosal atrophy in functioning (proximal) colon, to parallel the disuse atrophy induced in the defunctioned (distal) colon. Animals remained on the diet throughout the experiment and were killed when moribund or at 40 weeks. At necropsy, the anatomical distribution, number, size and histological type of colon tumors were compared between functioning and defunctioned colonic segments within the same animal. At autopsy, there were significantly fewer colon tumors in the defunctioned segment (p less than 0.005). Furthermore, there were significantly fewer carcinomas (p less than 0.005) and fewer tumors greater than 1 cm diameter (p less than 0.01) in this segment. The data indicate that endogenous factors in the intestinal contents facilitate chemically-induced colon carcinogenesis. Luminal nutrition may be implicated. (Author abstract) (21 Refs)

6. EFFECTS OF GLUCOCORTICOID HORMONES ON CELL PROLIFERATION IN DIMETHYLHYDRAZINE-INDUCED TUMOURS IN RAT COLON.

Tutton PJ, Barkla DH
Dept. Anatomy, Monash Univ., Clayton, Victoria, 3168, Australia
Virchows Arch [Cell Pathol]; 38(2):247-251 1981

Adrenocortical hormones have previously been shown to influence cell proliferation in many tissues. In this report, their influence on cell proliferation in the colonic crypt epithelium and in colonic adenocarcinomata is compared. Colonic tumor cell proliferation was found to be retarded following adrenalectomy and this retardation was reversible by administration of hydrocortisone, or by administration of synthetic steroids with predominantly glucocorticoid activity. Tumor cell proliferation in adrenalectomized rats was not promoted by the mineralocorticoid hormone aldosterone. Neither adrenalectomy, nor adrenocortical hormone treatment, significantly influenced colonic crypt cell proliferation. (Author abstract) (21 Refs)

7. SEROTONIN UPTAKE INHIBITORS RETARD THE GROWTH OF SOME COLORECTAL TUMOURS (MEETING ABSTRACT).

Tutton PJ, Barkla D
Department of Anatomy, Monash University, Clayton, Australia
Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

This report concerns the effects of two serotonin uptake inhibitors, Citalopram and Fluoxetine, on colonic tumors. Cell proliferation rates in dimethylhydrazine (DMH)-induced rat colonic tumors were measured using a stathmokinetic technique. Growth rate of xenografted human colorectal tumors propagated in immune-deprived mice were also assessed. In DMH-induced rat colonic tumors both Citalopram and Fluoxetine strongly inhibited cell proliferation and in two out of three lines of human tumors, growth was also strongly inhibited by both these agents. In one tumor line growth remained inhibited for a treatment period of 30 days and during another 30 days following cessation of treatment only a minority of the xenografts re-grew. The response to serotonin uptake inhibitors lends direct support to the concept that colonic tumor cells, unlike jejunal or colonic crypt cells, have a serotonin uptake mechanism. Thus in normal intestinal epithelial cells, proliferation is stimulated by chemical messengers acting on surface membrane receptors, the messenger then being cleared from the region and signal to divide is terminated. By contrast, in tumors, mitosis appears to be promoted by chemical messengers that are taken into the malignant cell, where the messenger may not be subject to the normal clearance mechanisms, and hence the signal may persist and lead to the production of daughter cells, each a cytoplasmic supply of stimulating messenger substance. (no Refs)

8. THE INFLUENCE OF CARCINOGEN TREATMENT ON CELL PROLIFERATION IN MOUSE COLONIC CRYPTS (MEETING ABSTRACT).

Kennedy MF, Tutton PJ, Barkla DH
Department of Anatomy, Monash University, Clayton, Australia
Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

The aims of the study were first, to observe the effect of treatment with the colonic carcinogen 1,2-dimethyl-hydrazine (DMH) on cell proliferation in mouse colon, and secondly to investigate the factors regulating proliferation in normal and DMH-treated colon. One-mo-old male mice were given weekly subcutaneous injections of DMH for 15 wk, and were then used in experiments within three wk of the final injection. Estimates of mitotic rates were obtained by a stathmokinetic technique, using vinblastine as the metaphase-arrest agent. The results show that DMH-treatment produced a significant increase in the rate of cell proliferation of colonic animals, cell proliferation was most rapid in the second lowest fifth of the crypt, whereas in DMH-treated animals the compartment of most rapid cell proliferation was elevated to the middle fifth of the crypt. The colonic crypts of both control and DMH-treated mice showed a reduction in mitotic rate following treatment with the alpha 2-adrenoceptor antagonist, Yohimbine. This reduction was equally distributed along the length of the crypts in both groups. The conclusions of the study are first, that DMH-treatment increases the mitotic rate in mouse colonic epithelium and also changes the site of most rapid cell proliferation to a higher level within the crypt. Secondly, it is apparent that at least one of the normal control mechanisms for regulating crypt cell proliferation in mouse colon, ie alpha 2 adrenoceptor-mediated inhibition, is maintained after DMH treatment. (no Refs)

9. ENHANCEMENT OF HYPERTHERMIA-INDUCED CYTOTOXICITY UPON ATP DEPRIVATION.

Laval F, Michel S

Radiobiologie Clinique (INSERM U 66), Institut Gustave Roussy, 9 48 00 Villejuif, France

Cancer Lett; 15(1):61-65 1982

The combined effects of hyperthermia and uncouplers of oxidative phosphorylation on mammalian cell survival were studied in vitro. Uncouplers studied were dinitrophenol (DNP), m-chlorocarbonylcyanide phenylhydrazone (CCCP), and 5-thio-d-glucose (5-TG). H4 cells derived form rat hepatoma cells were used for the experiments. All heat treatments were at 41 C. Uncouplers were toxic towards cells treated under aerobic conditions at 41 C. 5-TG potentiated the effect of hyperthermia in the hypoxic cells. In aerobic conditions the intracellular ATP concentration decreased in the presence of uncouplers. Similar changes occurred in hypoxic cells treated with 5-TG. Decrease in viability was observed when the cells were incubated at 41 C in the presence of CCCP, although this compound shows low toxicity at 37 C. The lethality of cells at 41 C incubated with DNP is not due to the compound alone because the concentration used shows low toxicity towards the cells at 37 C. The intracellular ATP concentrations were determined after 5-hr incubation with each compound studied. Results show that the thermal sensitivity of H4 cells increases at low ATP concentrations and is related to the potency of the inhibitor. The decrease in survival is directly related to the ATP concentration regardless to the drug used. (19 Refs)

10. INDUCTION OF RAT COLONIC EPITHELIAL ORNITHINE DECARBOXYLASE (ODC) BY BILE SALTS, AND ITS ENHANCEMENT BY COLON CARCINOGENS PRETREATMENT (MEETING ABSTRACT).

Takano S, Akagi M, Bryan GT

Department of Surgery, Kumamoto University, Kumamoto, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

A single intrarectal (ir) instillation of bile salts, presumptive colon promoters, results in a significant, early transient dose-response induction of rat colonic polyamine biosynthetic enzymes, ODC and S-adenosyl-L-methionine decarboxylase. Pretreatment by ir N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) or sc dimethylhydrazine (DMH) 1 wk before bile salt treatment enhanced and prolonged deoxycholate-induced ODC levels. This enhancement was dependent on pretreatment dose of MNNG, and was observed up to 3 mo after MNNG pretreatment. These data suggest that induced colonic ODC activity by bile salts may be related to colon carcinogenesis in a manner analogous to that shown to occur in mouse skin tumor systems. (no Refs)

11. GYROMITRIN AS A TUMOR INDUCER.

Toth B, Patil K
Eppley Inst. Res. Cancer and Allied Diseases, Univ. Nebraska Medical Center, Omaha, NE, 68105
Neoplasma; 28(5):559-564 1981

Gyromitrin (acetaldehyde methylformylhydrazone) was administered in propylene glycol as 12 weekly subcutaneous injections of 50 ug/g weight to randomly bred Swiss mice. The treatment induced lung and preputial gland tumors in incidences of 51 and 0% in females and 46 and 28% in males, respectively. In the propylene glycol injected control groups, the corresponding tumor incidences were 28 and 0% in females and 32 and 0% in males. Histopathologically, the tumors were classified as adenomas and adenocarcinomas of the lungs and squamous cell papillomas and carcinomas and adenocarcinomas of preputial gla nds. Gyromitrin is an ingredient of the wild edible false morel mushroom Gyromitrin esculenta. The environmental significance of the findings is discussed. (Author abstract) (26 Refs)

12. THE DIFFERENCE OF 3H-THYMIDINE UPTAKE AMONG 5 FU OR 5 FU COMBINED WITH NCS TREATED AND NOT TREATED GROUPS OF DHPN-INDUCED PANCREATIC CANCER IN HAMSTERS (MEETING ABSTRACT).

Miyazaki K
First Department of Surgery, Kyoto University School of Medicine, Kyoto, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

One of the most remarkable features of cancer cells is autochthonous increased proliferation. This experiment was done to clarify the increase of 3H-thymidine uptake in dinitrophenylhydrazine (DHPN) induced pancreatic cancer and its decrease by the therapeutic effect of 5-fluorouracil (5 FU) and Neocarcinostatin (NCS). Thirty-five female and 35 male hamsters were administered DHPN 500 mg/kg body wt, sc weekly and 5 females and 5 males vehicle only. After 13 wk, 20 females and 20 males were administered 5 FU 1 mg ip qod. In 10 females and 10 males 5 FU was combined with 2 mg NCS ip. Seventeen, 18 and 19 wk later, radioactivity ie cpm of 3H-thymidine/DNA concentration in DHPN-induced pancreatic cancer was revealed to be increased vs control pancreases by liquid scintillation spectrometry. Uptake of 3H-thymidine was decreased in the 5 FU group and most in the NCS group. (no Refs)

13. CHRONIC INHALATION TOXICITY OF HYDRAZINE: ONCOLOGENIC EFFECTS.

MacEwen JD, Kinkead ER, Vernot EH, Haun CC, Hall A
California Univ., Dayton, OH
Chronic Inhalation Toxicity of Hydrazine: Oncologenic Effects. Available from National Technical Information Service, Springfield, VA, as AD-A101 847/2:, 67 pp., 1981.

Year-long exposures of animals were conducted to hydrazine in the listed concentrations: 0.05, 0.25, 1.0, 5.0 ppm - rats and hamsters; 0.05; 0.25, 1.0 ppm - mice; and 0.25, 1.0 ppm - dogs. Hamsters were held 1 year postexposure, rats -18 months postexposure, mice 15 months postexposure and dogs -38 months postexposure. Hamsters exposed to the higher concentration showed pathologic changes characteristic of degenerative disease while rats exhibited changes in respiratory epithelium related to chronic irritation. After exposure to 5.0 ppm hydrazine, hamsters developed a 10% incidence of benign nasal polyps compared to 0.5% in controls. Male and Female rats showed dose-dependent incidences of microscopic benign epithelial nasal tumors and small numbers of microscopic malignant epithelial nasal tumors after 1 year exposure to hydrazine and 18 months postexposure holding. (Author abstract)

HETEROCYCLIC COMPOUNDS

14. MUTAGEN AND ANTI-MUTAGEN IN GINGER, ZINGIBER OFFICINALE.

Nakamura H, Yamamoto T
Biological Inst., Konan Univ., Kobe 658, Japan
Mutat Res; 103(2):119-126 1982

Rhizome juice of ginger contains compounds that both enhance and suppress the mutagenic action of 2(2-furyl)-3-(5-nitro-2-furyl)acryl amide (AF2) and N-methyl-N'-nitro-N-nitrosoguanidine (NTG) on Escherichia coli B/r (strain Hs30). The clear supernatant of filtered, centrifuged mashed rhizome increased the apparent mutagenic effects of AF2 and NTG as determined by reversions to arginine independence of E coli. Diethyl ether extraction of ginger juice, followed by chromatographic separation and mutagenicity tests, revealed that the factor enhancing mutagenesis by AF2 was (6)-gingerol. The same compound also enhanced NTG mutagenicity, and caused reversions and death of bacteria in a concentration-dependent way. The water-soluble and boundary fractions of an ether/water separation of ginger rhizome juice suppressed the mutagenesis of (6)-gingerol, which remained in the ether fraction. It is suggested that (6)-gingerol may be activated by specific mutagens only, which explains why antimutagenic agents in the rhizome juice were effective in some experiments and not in others. (10 Refs)

15. REDUCTION BY FUMARIC ACID OF CARCINOGENIC AND TOXIC EFFECTS OF 5-NITROFURAN NAPHTHYRIDINE DERIVATIVE (NFN) (MEETING ABSTRACT).

Kuroda K, Kanisawa M, Akao M
Chiba University, Chiba, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Feeding ICR mice with 0.012% NFN diet for 14 wk induced a high incidence of tumors ie squamous cell carcinomas and papillary adenomas of forestomachs in 3 and 9 of 12 mice, respectively, and papillary adenocarcinomas of lungs in all mice. Subsequent feeding with 1% fumaric acid diet reduced effectively the tumor incidence. No tumors developed in forestomachs of all 13 mice, and papillary adenocarcinomas of lungs in 6 of 13 mice. The ameliorating activity of fumaric acid against toxic effects of NFN were also shown in vitro in cultures of mouse and chick embryo cells. (no Refs)

16. CIRCADIAN VARIATION IN THE SUSCEPTIBILITY OF MOUSE EPIDERMIS TO CHEMICAL CARCINOGENS.

Iversen OH, Kauffman SL
Inst. Pathology, Univ. Oslo, Rikshospitalet, Oslo 1, Norway
Int J Chronobiol; 8(1):49-62 1981

Groups of hairless mice were given a single topical application of each of two highly-reactive carcinogens (methylnitrosourea and beta-propiolactone) at 12(00) and 00(00). The tumor yield was as follows: for methylnitrosourea there was a slightly higher yield of skin tumors in the animals painted at 12(00); for animals painted with beta-propiolactone, there was a significantly higher skin tumor yield in those painted at 12(00). When the groups painted with the two carcinogens are considered together, there was a significantly higher number of animals with all types of tumors in the group painted at 12(00). Hence, there seems to be a circadian variation in the sensitivity of a tissue to a single contact with a chemical carcinogen. This may be related to the proliferative state of the tissue involved: at 12(00), DNA and cell division takes place at a more rapid rate than at 00(00). (Author abstract) (30 Refs)

17. MORPHOLOGY OF EARLY CHANGES IN LIVER CARCINOGENESIS INDUCED BY METHAPYRILENE.

Reznik-Schuller HM, Lijinsky W

Chemical Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701

Arch Toxicol; 49(1):79-83 1981

Two wk of treatment with the liver carcinogen methapyrilene induced a significant increase in mitochondria of periportal hepatocytes in F344 rats. Administration of [3H]-methapyrilene hydrochloride resulted in a pronounced concentration of bound radioactivity in the periportal hepatocytes, with mitochondria being the principal site of intracellular binding. The nuclei of the liver cells were unlabeled. (Author abstract) (8 Refs)

INORGANIC AGENTS AND PARTICULATES INCLUDING FIBERS

18. BIOLOGICAL EFFECTS OF INGESTED AMOSITE ASBESTOS, TACONITE TAILINGS, DIATOMACEOUS EARTH AND LAKE SUPERIOR WATER IN RATS.

Hilding AC, Hilding DA, Larson DM, Aufderheide AC

(c/o Larson) Dept. Pathology and Lab. Medicine, Sch. Medicine, Univ. Minnesota-Duluth, Duluth, MN, 55812

Arch Environ Health; 36(6):298-303 1981

Because amphibole fibers were found in Lake Superior and in Duluth municipal water, this study was initiated to evaluate the carcinogenicity of ingested asbestos. Groups of 22-30 Sprague-Dawley rats were fed asbestos and related materials during their lifetime and were examined at autopsy after spontaneous death. Test materials were unfiltered Duluth city tap water, municipal water reservoir sediment suspension, taconite plant tailings, amosite asbestos (a 'low-dose' group at 20 mg/rat/day and a high-dose group at 300 mg/rat/day) and diatomaceous earth; a control group drank fiber-free well water or filtered city tap water. Autopsy studies revealed no significant increase in the incidence of malignant tumors in any experimental group compared with that in the control group. (Author abstract) (50 Refs)

19. SURFACE REDUCTION OF AMORPHOUS NIS PARTICLES POTENTIATES THEIR PHAGOCYTOSIS AND SUBSEQUENT INDUCTION OF MORPHOLOGICAL TRANSFORMATION IN SYRIAN HAMSTER EMBRYO CELLS.

Heck JD, Costa M
Div. Toxicology, Dept. Pharmacology, Univ. Texas Medical Sch. at Houston, P. O. Box 20708, Houston, TX, 77025
Cancer Lett; 15(1):19-26 1982

The proportion of transforming activity of particulate nickel compounds to their phagocyte uptake was studied. Surface reduction of amorphous NiS particles with LiAlH4 increased phagocytosis and the incidence of morphological transformation concomitantly. The incidence of morphological transformation following exposure of Syrian hamster embryo (SHE) cells to crystalline alphaNiS particles was considerably greater than that following a similar exposure to amorphous NiS particles. Increased uptake was observed in solvent-cleaned and surface-reduced crystalline alphaNiS particles. Chemical reduction of the amorphous NiS particles' surface with LiAlH4 resulted in increase both in their phagocytic uptake by Chinese hamster ovary cells and in their ability to induce transformation in SHE cells. The phagocytosis and transforming activity of crystalline alphaNiS particles was also enhanced by LiAlH4 reduction. The results are consistent with previous observations showing that untreated crystalline NiS particles have a negative surface charge while amorphous NiS particles possess positively charged surfaces. The transforming activity of particulate metal compounds is proportional to their phagocytic uptake. The entry of metal sulfide particles is related to their surface properties and to the degree of negative charge on the surface microenvironment. (27 Refs)

20. HEALTH HAZARDS OF ASBESTOS EXPOSURE.

Kaw JL
Industrial Toxicology Res. Centre, Lucknow 226 001, India
J Sci Ind Res; 40(5):342-346 1981

The industrial and environmental sources, pathologic and histologic manifestations, and carcinogenic role of asbestos are reviewed. Pulmonary fibrosis and pleural plaques found in lungs of persons exposed to asbestos dust are discussed. Suggested chemical and physical basis of the carcinogenic role of asbestos is reviewed. (109 Refs)

21. THE INDUCTION OF DNA STRAND BREAKAGE BY NICKEL COMPOUNDS IN CULTURED CHINESE HAMSTER OVARY CELLS.

Robison SH, Costa M
Div. Toxicology, Dept. Pharmacology, Univ. Texas Medical Sch. Houston, P. O. Box 20708, Huston, TX, 77025
Cancer Lett; 15(1):35-40 1982

The effects of nickel chloride and crystalline NiS on the DNA of cultured Chinese hamster ovary (CHO) cells were studied by using alkaline sucrose gradient analysis. Both NiCl2 and crystalline alphaNiS induced DNA strand breaks in cultured CHO cells. Single strand breaks were detected in cells treated with either toxic or non-toxic levels of crystalline alpha NiS. Exposure to alpha NiS at 1 ug/ml for 24 hr does not interfere with the division of CHO cells. The level of cell plating efficiency was essentially similar to that of untreated cultures. This concentration caused substantial DNA strand breaks suggesting that crystalline alpha NiS selectively damages DNA. The positional shift in gradient sedimentation of the radiolabelled DNA fragments isolated from cells treated with either 1 ug.ml, or 5 ug/ml, or 20 ug/ml crystalline alphaNiS indicated the concentration-dependent effect on DNA strand breaks. Treatment of cells with NiC 12 at 1ug/ml, or 10 ug/ml also resulted in single strand breaks after only 2-hr exposure. Results suggest that nickel compounds which cause cellular transformation have highly selective and specific effects upon DNA structure since DNA strand breakage occurred at such low concentrations. (22 Refs)

22. SELECTIVE EFFECT OF THE METALLOCARCINOGEN BERYLLIUM ON HORMONAL REGULATION OF GENE EXPRESSION IN CULTURED CELLS.

Perry ST, Kulkarni SB, Lee KL, Kenney FT
Univ. Tennessee-Oak Ridge Graduate Sch. Biomedical Sciences, Oak Ridge, TN, 37830
Cancer Res; 42(2):473-476 1982

Effects of the metallocarcinogen beryllium on regulation of gene expression were assessed by analysis of hormonal regulation of synthesis of tyrosine aminotransferase in beryllium-treated hepatoma cell cultures. Cell growth was not affected by exposure of the cells to 1 uM BeSO4 throughout their 4-to 5-day growth cycle. In cells pretreated in this way, the induction by glucocorticoids was specifically impaired, the extent of induced enzyme synthesis being reduced about 50%. Inductions by insulin or cyclic adenosine 3':5'-monophosphate were not influenced by the metal. The results suggest that low concentrations of beryllium selectively interfere with regulatory mechanisms controlling transcriptional events in gene expression. (Author abstract) (24 Refs)

23. INDUCTION, CHARACTERIZATION AND ISOLATION OF PRENEOPLASTIC HEPATOCYTES AFTER COMBINED TREATMENT WITH 2-ACETYLAMINOFLUORENE AND FERRIC NITRILOTRIACETATE.

Bibbiani C, Malvaldi G
Istituto di Patologia Generale, Universita di Pisa, Pisa, Italy
Boll Soc Ital Biol Sper; 57(16):1722-1726 1981

Male rats (Sprague-Dawley, 80-90 g) were administered for 8 wk ferric nitrilotriacetate (Fe-NTA; 0.5 ml/100 g/day ip) and 2-acetaminofluorene (2-AAF; 300 mg/kg standard diet without antioxidants). Control animals were administered the same dose of Fe-NTA. One wk after the end of treatment, liver was perfused in situ with Hanks soln without Ca. Two liver tissue specimens were removed for histological and histochemical testing. Liver perfusion was followed with collagenase, and at the end of perfusion, hepatocytes were removed by bland mechanical treatment. Part of the suspension was used to prepare smears and for biochemical testing, the rest was further purified. Partial separation of different cells was accomplished by isopycnic gradient separation. Combined administration of Fe-NTA and 2-AAF induced formation of small nodules or areas made of HC without iron that can be easily identified due to the absence of pigment. Gamma glutamyltranspeptidase activity was demonstrated in areas without iron, while glucose-6-phosphatase activity disappeared. (15 Refs) (In ITA)

24. MODIFICATION OF MAMMARY CARCINOGENESIS AND TISSUE PEROXIDATION BY SELENIUM DEFICIENCY AND DIETARY FAT.

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Dept. Breast Surgery and Breast Cancer Res. Unit, Roswell Park Memorial Inst., Buffalo, NY
Nutr Cancer; 2(3):136-142 1981

The independence of selenium (Se) and unsaturated fat intake as modifiers of the incidence of mammary tumors induced by 7,12-dimethylbenz(a)anthracene (DMBA) and the liability of mammary tissue to lipid peroxidation were studied. Female Sprague-Dawley rats were fed one of six synthetic diets (three different types of diets with and without Se supplementation) from weaning until termination of the experiment. The three basal diets contained different levels of tocopherol-stripped corn oil, 1%, 5%, and 25%. Mammary tumors were induced by intragastric administration of a 5 mg dose of DMBA at 50 days of age. Measurement of Se-dependent glutathione peroxidase activity in the rat liver was used to determine the functional status of Se at 0, 10, 20, and 30 days after the rats were given either the basal Se-deficient diet or the supplemented regimen. In rats receiving an adequate supplement of Se (0.1 ppm) tumor incidence increased proportional to the amount of corn oil in the diet. A deficiency of Se in the diet resulted in a marked enhancement in tumor incidence and yield in rats fed the 25% corn oil regimen. Glutathione peroxidase activity in the mammary gland was not influenced by dietary fat but was severely depressed in the absence of added Se. Lipid peroxidation in the mammary tissue was elevated with increasing levels of dietary fat in rats supplemented with 0.1 ppm of Se. The unsupplemented 25% fat group showed significant enhancement of tissue peroxidation when compared to their supplemented controls. Determination of peroxide in the synthetic diets demonstrated that corn oil when mixed with the other ingredients, auto-oxidized very quickly especially at room temperature. The amount of peroxide formed is proportional to the content of corn oil and to the length of storage. Se deprivation did not affect the tumor growth rate or the proliferation of malignant vs benign lesions. (40 Refs)

AMIDES, CARBAMATES AND UREAS

25. TRANSPLANTATION EXPERIMENTS WITH LEUKAEMIA CAUSED BY CHEMICAL CARCINOGENS (MEETING ABSTRACT).

Ember I
University Medical School, Debrecen, Hungary
Ninth Congress of the Haematological Society, October 1-3, 1981, Debrecen, Hungary. The Society 175 pp., 1981.

Bojan and Kertai using urethane and diethylstilbestrol caused acute lymphoid leukemia in C3H/He mg/Lati x AKR/Lati F1 hybrid females, which was also characterized by the tumorous infiltration of the ovaries. Splenic and ovarial cell-suspensions prepared of leukemic animals were used by the author for grafting leukemia into newborn and adult C3H and AKR mice, as well as into newborn and adult R/A rats. In newborn females, (C3H, AKR, R/A) besides leukemia, tumor of the ovary also developed. In adult AKR mice (male and female) only leukemia developed, while adult C3H females developed lymphosarcoma involving both ovaries and lymph nodes. Adult C3H males and R/A rats remained free from leukemia. Significant differences between the effect of the two cell-suspensions couldn't be observed. (no Refs)

26. EFFECT OF MAJOR HISTOCOMPATIBILITY GENE COMPLEX (MHC) ON THE SUSCEPTIBILITY TO URETHANE INDUCED LUNG TUMORS IN MICE (MEETING ABSTRACT).

Moriwaki K, Miyashita N

Department of Cytogenetics, National Institute of Genetics, Mishima, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

In addition to a pulmonary tumor resistance (ptr) gene probably located on chromosome 11, MHC seems to function in the processes of tumorigenesis. This study aims to reveal the effect of MHC on urethane-induced lung tumor incidence. In susceptible A/J mouse, av foci of lung tumor is 28.0. If H-2a complex of A/J is replaced by H-2b or H-2s, tumor foci reduce to about 10. These results clearly showed the profound regulatory function of MHC for the lung tumor development by urethane in mouse strains with susceptible ptr gene. Suppressive effect of wild-derived chromosomes is also investigated. (no Refs)

27. INHIBITION OF 7,12-DIMETHYLBENZ[A]ANTHRACENE- AND URETHAN-INDUCED LUNG TUMOR FORMATION IN A/J MICE BY LONG-TERM TREATMENT WITH DEHYDROEPIANDROSTERONE.

Schwartz AG, Tannen RH

Fels Res. Inst. and Dept. Microbiology, Temple Univ. Medical Sch., Philadelphia, PA, 19140

Carcinogenesis; 2(12):1335-1337 1981

Long-term treatment with the adrenal steroid dehydroepiandrosterone reduces weight gain without suppressing appetite and inhibits the occurrence of 7,12-dimethylbenz[a]anthracene- and urethan-induced lung tumors in A/J mice. (Author abstract) (26 Refs)

28. EFFECT OF PHENOBARBITAL ON CHEMICALLY-INDUCED NEOPLASMS, MALFORMATIONS AND DOMINANT LETHALS IN MICE (MEETING ABSTRACT).

Gotoh H, Nomura T, Shibata K, Hata S, Enomoto T, Kusafuka T, Miyamoto S, Sakamoto Y

Department of Fundamental Radiology, Osaka University School of Medicine, Osaka, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Phenobarbital (40-80 ug/g, sc) pretreatment of young adult and adult ICR/Jcl mice greatly diminished lung tumorigenesis initiated by urethane, furylfuramide (AF-2), and 7,12-dimethylbenz(a)anthracene (DMBA), while phenobarbital pretreatment enhanced embryo toxicities initiated by urethane, dimethyl-nitrosamine, 4-nitroquinoline-1-oxide, AF-2, and aminopyrine, but did not affect x-ray-induced ones. DMBA-induced dominant lethals were also enhanced by phenobarbital pretreatment. (no Refs)

29. ENHANCING EFFECT OF BARBITAL ON N-2-FLUORENYL-ACETAMIDE INDUCED RAT LIVER LESION S (MEETING ABSTRACT).

Tanaka T, Mori H, Nishikawa A, Takahashi M

Department of Pathology, Medical Gifu University, Gifu, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Comparison of enhancing effects of phenobarbital (PB) and barbital (B) in hepatotumorigenesis was examined by quantitative analysis of the behavior of altered foci following discontinuation of N-2-fluorenylacetamide (FAA) administration. Thirty-four male ACI rats of 2 mo old were fed 0.02% FAA diet for 13 wk and some of them were sacrificed immediately. Remaining rats were divided into three groups and given a basal diet (Group I) or 0.05% PB diet (Group II) or 0.05% B diet (Group III) and sacrificed sequentially at 8 and 16 wk after the beginning of administration of each diet. The number of altered foci detected in hematoxylin and eosin or iron stain specimen/cm2 of the liver space at 16 wk of Group I remarkably decreased compared to that at termination of FAA feeding. However, the number of Group II or III was similarly maintained at 8 and 16 wk and the number at 16 wk of both groups was significantly higher than that of Group I. These data show that B like PB could be an enhancer in hepatotumorigenesis. (no Refs)

30. LAPAROSCOPIC CHANGES OF THE LIVER DURING HEPATOCARCINOGENESIS FED WITH 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE OR 2-FLUORENYLACETAMIDE (MEETING ABSTRACT).

Numa Y, Okita K, Ando K, Fukumoto Y, Kodama T, Takemoto T

1st Department of Internal Medicine, Yamaguchi University School of Medicine, Ube, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The hyperplastic liver nodule has been focused as the precancerous lesion in rats during hepatocarcinogenesis. However, there is not any direct evidence that hepatoma is exactly induced in this nodule. Therefore, we applied the laparoscopic method to observe the course during hepatocarcinogenesis. The small diameter fiberscope (diameter 4 mm) and rigid laparoscope were made by the courtesy of Machida Co (Tokyo). Moreover, a biopsy method under direct vision was devised for the consecutive histological study of the nodules. Tentatively, laparoscopy revealed 2 kinds of nodules showing red or gray with or without vessels on their surface. Moreover, the biopsied specimen was sufficient to analyze biochemical multiplicity of the nodules. (no Refs)

31. CHEMICALLY-INDUCED UNSCHEDULED DNA SYNTHESIS IN PRIMARY RAT HEPATOCYTE CULTURES: A COMPARISON WITH BACTERIAL MUTAGENICITY USING 218 COMPOUNDS.

Probst GS, McMahon RE, Hill LE, Thompson CZ, Epp JK, Neal SB
Div. Toxicology, Lilly Res. Laboratories, Greenfield, IN, 46140
Environ Mutagen; 3(1):11-32 1981

Hepatocyte primary culture (HPC)-DNA repair test using a relatively large number of compounds representing a wide variety of chemical classes is discussed. Over 200 compounds were tested for induction of unscheduled DNA synthesis (UDS) and the results were correlated with bacterial mutagenicity using a modified Ames test. A positive response was seen in both systems with many procarcinogens and ultimate carcinogens while compounds believed to be noncarcinogens were inactive. Recognized carcinogens/mutagens were readily detected by the two systems. Structurally realted noncarcinogens produced negative results in both systems. The modified Ames test and the HPC-UDS repair test were sensitive to compounds capable of interacting with DNA, and represent acceptable tests for genotoxic substances. The induction of UDS in hepatocytes showed good correlation with bacterial mutagenesis in response to polycyclic aromatic hydrocarbons, aromatic amines, biphenyls, nitrosamines, carbamates, azo-compounds, acridines, halogenated compounds, nitrosoureas, quinolines, pyridines, purines, pyrimidines, esters, and carbamates. Nitrocompounds although active in bacteria, were poor inducers of UDS. Results support the complementary and confirmatory nature of the tests for genotoxic chemicals and indicate the usefulness of the hepatocyte UDS system as a component in a battery of short-term predictive tests for mutagens/carcinogens. (45 Refs)

ALIPHATIC HALOGEN COMPOUNDS

32. PATTERN OF GLYCOGEN AND IRON ACCUMULATION IN EARLY APPEARING BHC INDUCED LIVER LESIONS AND LIVER TUMOURS.

Nigam SK, Babu KA, Bhatt DK, Karnik AB, Thakore KN, Lakkad BC, Kashyap SK, Chatterjee SK
Natl. Inst. Occupational Health, Ahmedabad 380016, India
Indian J Med Res; 74:289-296 1981

Inbred Swiss mice were fed diet containing 500 ppm of technical grade BHC (hexachlorocyclohexane) for 8 mo when typical liver tumor developed. Animals were weighed at the start of the experiment and prior to sacrifice. These animals were sacrificed at different time intervals and their liver was weighed to find out the liver weight as a percentage of body wt. The liver wt increased with increased duration of BHC feeding. Liver sections were examined for glycogen and iron accumulation. In normal liver glycogen was uniformly distributed, in the hepatocytes; after BHC feeding glycogen deficient cells around central vein and excessively glycogen laden liver cells were seen in the periphery. Glycogen in these cells remained in excess even after withdrawing BHC feeding. In 6 mo tumor developed in the liver and tumor cells were completely deficient of glycogen. Similarly iron was uniformly distributed in Kupffer cells and in hepatocytes in normal liver. In hyperplastic areas Kupffer cells contained minimum iron and the tumor cells were completely deficient of iron. Thus glycogen and iron distribution followed a definite pattern on exposure to BHC. (Author abstract) (16 Refs)

33. STUDIES ON GLUCOSE-6-PHOSPHATE, FRUCTOSE-1,6-DIPHOSPHATASE ACTIVITY, GLYCOGEN DISTRIBUTION AND ENDOPLASMIC RETICULUM CHANGES DURING HEXACHLOROCYCLOHEXANE INDUCED HEPATOCARCINOGENESIS IN PURE INBRED SWISS MICE.

Karnik AB, Thakore KN, Nigam SK, Babu KA, Lakkad BC, Bhatt DK, Kashyap SK, Chatterjee SK
Natl. Inst. Occupational Health (ICMR), Meghani Nagar, Ahmedabad - 380 016, India
Neoplasma; 28(5):575-584 1981

Inbred Swiss mice were fed hexachlorocyclohexane (BHC) at 500 ppm dose level in diet for 2, 4, 6 and 8 months. Later BHC was discontinued for 4 months and subsequently the animals were refed BHC for 1 month. Glucose-6-phosphatase (G6Pase) and fructose-1,6-diphosphatase (FDPase) activity was studied at different time intervals accompanied with changes in glycogen distribution and endoplasmic reticulum (ER) proliferation in hepatocytes. G6Pase and FDPase showed a decline in activities on BHC feeding. The activities of these enzymes showed recovery on BHC discontinuation. The changes were progressive with duration of exposure. After 6 months exposure the biochemical changes became more resistant to recovery. Maximal changes occurred in 8 month-exposure and the changes were irreversible. Glycogen accumulation and depletion followed a definite pattern. After 2 months of BHC feeding, increase in parenchymal glycogen storage zones was observed. In the later stage of hepatocarcinogenesis and especially in tumors, glycogen was depleted considerably. Smooth endoplasmic reticulum (SER) proliferation was recorded around the 3rd and 4th month. The correlation between glycogen accumulation, SER proliferation, G6Pase and FDPase activity is discussed. (Author abstract) (31 Refs)

34. SENSITIVITY OF DROSOPHILA MELANOGASTER TO LOW CONCENTRATIONS OF GASEOUS MUTAGENS: III. DOSE-RATE EFFECTS.

Kale PG, Baum JW
Safety and Environmental Protection Div., Brookhaven Natl. Lab., Upton, NY, 11973
Environ Mutagen; 3(1):65-70 1981

Sex-linked recessive lethal mutations were induced in Drosophila melanogaster males by chronic and acute exposures to gaseous 1,2-dibromoethane (DBE) in the range of 2.3-31.0 ppm/hr. Acute treatments corresponding to each chronic treatment were made by increasing concentration approx 30x with concomittant decrease in exposure period. Canton-S and Basc strains of D melanogaster were used to detect the mutations. Germ cell targets sampled, in order of decreasing sensitivity, were spermatocytes, spermatids, and spermatozoa. Total number of chromosomes tested and mutations confirmed in each daily brood for acute exposure, including previous data from chronic exposure at each of four exposure levels (EL) are presented. Each type of germ cell was tested in the immature and mature stage. No consistent pattern of difference was observed between acute and chronic exposure for three of the four EL. At the highest EL (30-31 ppm/hr), a consistent difference was observed between chronic and acute EL. At the higher EL in all three germ cells stages, the acute exposure showed significant increase in mutation frequency over chronic exposure. The greater acute vs chronic mutation frequency for spermatozoa, a metabolically inactive cell stage, indicates that the exposure rate effect at high EL levels is due to systemic factors such as metabolic deactivation or elimination, rather than repair of permutational damage in the target cells. The significance of these findings in risk assessment for environmental pollutants is discussed. (9 Refs)

35. RELATIONSHIPS BETWEEN MICROSOMAL METABOLISM, DNA DAMAGE AND ADDUCT BINDING IN POLYCYCLIC HYDROCARBON-EXPOSED LUNG (MEETING ABSTRACT).

Haski R, Stewart BW
Department of Pathology, University of New South Wales, Kensington, Australia
Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

Preparations of isolated lung DNA from rats treated by intra-tracheal instillation of 3-methylcholanthrene (3MC) may be distinguished from control preparations by the extent of structural damage to the nucleic acid. In the study to be described, damage to DNA was determined by benzoylated-diethylaminoethyl cellulose chromatography. To analyze the relationship between metabolism of 3MC and subsequent DNA damage, the effect of modifiers of cytochrome P-450 (P-450) on both parameters was examined. Initially, measurement was made of P-450 content of rat lung at various times after administration of the hydrocarbon. In this manner experimental conditions for the use of an inducing dose of 3MC were determined and criteria were available to examine the efficacy of carbon tetrachloride-inhalation as a means of inhibiting 3MC metabolism. Animals were then treated either with an inducing dose of 3MC or by prior exposure to carbon tetrachloride to perturb microsomal metabolism of the carcinogen. The subsequent effect, on 3MC-induced DNA damage and repair, was determined. In addition, the co-valent binding of 3MC to lung DNA was assayed using LH-20 chromatography. The findings indicate that the extent of polycyclic hydrocarbon-induced DNA damage in lung may be subject to wide variation as a consequence of exposure to agents which modifiy the rate of carcinogen metabolism. (no Refs)

POLYHALOGENATED RING COMPOUNDS INCLUDING INSECTICIDES

36. SEX DIFFERENCE IN ENHANCEMENT OF GGTASE-POSITIVE FOCI BY HEXACHLOROBENZENE AND LINDANE IN RAT LIVER.

Pereira MA, Herren SL, Britt AL, Khoury MM
Health Effects Res. Lab., U. S. Environmental Protection Agency, Cincinnati, OH, 45268
Cancer Lett; 15(1):95-101 1982

The ability of hexachlorobenzene (HCB) and lindane (LN) in diethylnitrosamine (D ENA) pretreated rats to enhance the incidence of gamma-glutamyltranspeptidase (GGTase)-positive foci was determined. Male and female Sprague-Dawley rats (175-225 g) were used in the experiments. HCB and LN increased the incidence of DENA and initiated GGTase-positive foci in rat liver. Animals that received a partial hepatectomy or sham operation, and then were given HCB or LN in their diet, developed relatively few GGTase-positive foci. When DENA was administered 24 hr after the partial hepatectomy, as compared to the sham operation, there was a slightly increased incidence of GGTase-positive foci. In female rats that received either a partial hepatectomy or sham operation followed by DENA, HCB and LN increased the incidence of GGTase-positive foci. In male rats, HCB and LN increased the incidence of GGtase-positive foci only when a partial hepatectomy preceded the DENA. The enhancement of GGtase-positive foci by HCB and LN was greater in female, compared to male rats. The results suggest that hepatocarcinogenicity of HCB and LN results in tumor promotion. (33 Refs)

37. URINARY METABOLITES OF 3,3'-DICHLOROBENZIDINE AND THEIR MUTAGENICITY.

Tanaka KI
Toray Shiga Hosp., 7-35, Sonoyama 2-chome, Otsu 520, Japan
Sangyo Igaku; 23(4):426-427 1981

3,3'-dichlorobenzidine (DCBZ) was administered to rats, urinary metabolites of the DCBZ, 3,3'-dichloro-N-acetylbenzidine (N-AcDCBZ) and 3,3'-dichloro-N,N'-diacetylbenzidine (NN'-AcDCBZ), were observed in the urine of the rats, and mutagenicity of the DCBZ, N-AcDCBZ, and NN'-AcDCBZ was investigated using Salmonella typhimurium TA 98 and TA 100 and a revertant mutagenicity test. Spectrographic pure DCBZ was administered po (20 mg) to five rats (Group 1), per trachea (10 mg) to five (Group 2), and pc (200 mg) to five (Group 3); five rats were not administered the DCBZ. DCBZ, N-AcDCBZ, and NN'-AcDCBZ were detected with both gas chromatography and high pressure liquid chromatography in the urine of Group 1 and 2 rats. Only NN'-AcDNBZ was observed in the urine of Group 3 rats. With the aid of Ames test, mutagenic activity of 1 ml urine samples containing N-acetyl DCBZ metabolites was shown to increase with the concentration of the metabolites in the urine samples from the Group 1 and 2 rats, but no mutagenic activity was observed for the 1 ml samples from the Group 3 rats. The mutagenic activity of the NN'-AcDCBZ was much lower than that of the DCBZ or the N-AcDCBZ. These techniques were thought to be applicable for study of mechanisms of carcinogenicity of these metabolites as well as for biological monitoring of the substances. (7 Refs) (In JPN)

38. 2,4-DICHLOROPHENOXYACETIC ACID - A NEW ENVIRONMENTAL MUTAGEN.

Khalatkar AS, Bhargava YR
Post-Graduate Dept. Botany, Nagpur Univ. Campus, Nagpur 440 010, India
Mutat Res; 103(2):111-114 1982

The mutagenic and teratogenic potential of 2,4-dichlorophenoxyacetic acid (2,4-D) were tested on barley (Hordeum vulgare) seeds at a concentration of 100 ppm. The compound did not affect markedly seedling height, but reduced germination and seed set. Other effects on the M1 generation included increased chromosomal aberrations, increased chlorophyll chimeras, and increased aberrant pollen mother cells and sterile pollen. In the M2 generation the chlorophyll-deficient mutations albina, viridis, chlorina, tigrina, striata, alboviridis, and viridoalba occurred, with tigrina types dominant (58-61%). While the mutagenic properties of 2,4-D demonstrated are potentially useful to breeders, caution is suggested in its use as an herbicide or hormone. (15 Refs)

39. LACK OF MUTAGENICITY OF THE FUNGICIDE 2,4,5,6-TETRACHLOROISOPHTHALONITRILE IN THE AMES SALMONELLA/MICROSOME TEST.

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Dept. Food Science and Human Nutrition, Univ. Florida, Gainesville, FL, 32611
Appl Environ Microbiol; 43(1):252-254 1982

The fungicide 2,4,5,6-tetrachloroisophthalonitrile was found to be not mutagenic to five Salmonella typhimurium tester strains. Incorporation of either a liver or a kidney activation system did not increase the mutagenic activity of the fungicide. (Author abstract) (14 Refs)

40. IMMUNOTOXICITY OF PENTACHLOROPHENOL (PCP): INCREASED SUSCEPTIBILITY TO TUMOR GROWTH IN ADULT MICE FED TECHNICAL PCP-CONTAMINATED DIETS.

Kerkvliet NI, Baecher-Steppan L, Schmitz JA
Sch. Veterinary Medicine, Oregon State Univ., Corvallis, OR, 97331
Toxicol Appl Pharmacol; 62(1):55-64 1982

Immune competence in mice following chronic dietary exposure to pentachlorophenol (PCP), and the effects of PCP exposure on susceptibility to virus infection and tumor growth, cytotoxic T-cell response, and macrophage phagocytic function in in vitro assays were examined. Adult male C57Bl/6 mice were fed diets containing 50 or 500 ppm pure (99+%) or technical grade (86%) PCP for 10-12 wk prior to assessment of immunocompetence. Exposure of mice to technical grade PCP resulted in enhancement of tumor susceptibility. The incidence of progressive methylcholanthrene (MCA)-induced transplanted tumors increased from 35% in controls to 67% in animals exposed to 50 ppm technical PCP and 82% in animals exposed to 500 ppm technical PCP. Mortality following primary Moloney sarcoma virus (MSV) inoculation and secondary MSV-transformed sarcoma cell (MSB) challenge increased from 19% in controls to 45% in animals exposed to 50 ppm technical PCP and 73% in animals exposed to 500 ppm technical PCP. An additional 50% of the MSV/MSB challenged mice exposed to 50 ppm technical PCP exhibited tumor dissemination into the spleen. Animals exposed to pure PCP did not exhibit enhancement of primary MCA- or MSV-induced tumor growth. Splenic tumor development was observed in 22% of the MSV/MSB challenged mice exposed to 50 ppm pure PCP, and in 44% of the MSV/MSB challenged mice exposed to 500 ppm PCP. Control mice did not develop splenic tumors. Significant depression in T-cell cytolytic activity and enhancement of macrophage phagocytosis in animals exposed to technical PCP were noted. No significant changes in in vitro immune response were noted with cells from pure PCP-exposed animals. (26 Refs)

41. DDT ACCELERATION OF MAMMARY GLAND TUMORS INDUCED IN THE MALE SPRAGUE-DAWLEY RAT BY 2-ACETAMIDOPHENANTHRENE.

Scribner JD, Mottet NK
Pacific Northwest Res. Foundation, 1124 Columbia St., Seattle, WA, 98104
Carcinogenesis; 2(12):1235-1239 1981

The compound 2-Acetamidophenanthrene (AAP) yields adducts to rat liver DNA and RNA in amounts comparable to those found for the potent hepatocarcinogen 2-acetamidofluorene, but is not hepatocarcinogenic. This suggested that AAP might initiate liver tumors, but was incapable of causing their progression to a detectable state. To test this hypothesis, the protocol devised by Peraino was used, in which 21-day-old male Sprague-Dawley rats were fed 0.02% AAP in a grain diet for 3 wk. This was followed by long-term feeding of 0.05% 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDT). The mean latent period of all tumors (primarily mammary tumors) was reduced about 6 mo by the DDT feeding. No tumors were found in rats treated with DDT only. Livers in all animals appeared normal at autopsy or on laparotomy, and showed barely detectable signs of toxicity upon histological examination. Thus, we have found that a once wide-spread environmental chemical acts as a tumor accelerator on a major target for human tumors. Because this finding is in the male rat, the significance of this result for breast cancer in women is uncertain. (Author abstract) (15 Refs)

42. METABOLISM OF DICHLOROBIPHENYLS BY HIGHLY PURIFIED ISOZYMES OF RAT LIVER CYTOCHROME P-450.

Kaminsky LS, Kennedy MW, Adams SM, Guengerich FP
Div. Lab. and Res., New York State Dept. Health, Albany, NY, 12201
Biochemistry; 20(26):7379-7384 1981

Hepatic mixed-function oxidase metabolism of the ubiquitous pollutant polychlorinated biphenyls (PCBs) is implicated in their toxification and detoxification. We used dichlorobiphenyls (DCBs) as models to investigate the effect of the chloro substituent sites on this metabolism experimentally and by molecular orbital calculations. Reconstituted, purified cytochrome P-450 PB-B and BNF-B, the major terminal oxidase isozymes of this system, from phenobarbital (PB)- and beta-naphthoflavone (BNF)-induced rats were used to investigate this metabolism. Both isozymes are also induced by PCBs. High-performance liquid chromatography (HPLC) was used to detect, quantify, and isolate metabolites. Metabolite structures were identified by mass spectrometry, dechlorination to identifiable hydroxybiphenyls, and HPLC retention times. All DCBs yielded 3-and 4- but no 2-monohydroxylated metabolites (3,3'-DCB also yielded a dihydroxy metabolite). Di-o-chloro-substituted DCBs were metabolized primarily by cytochrome P-450 PB-B, mono-o-chloro substituted DCBs by both isozymes approx equivalently, and DCBs without o-chloro substituents by BNF-B primarily. Thus PB-B preferentially metabolizes noncoplanar DCBs and BNF-B coplanar DCBs. The cytochrome isozymes exhibited differing regioselectivities for DCB metabolism-PB-B hydroxylated unchlorinated phenyl rings and BNF-B chlorinated rings. Incorporation of epoxide hydrolase yielded DCB dihydrodiols, and hydroxy metabolite patterns were consistent with those calculated from ring-opened arene oxide intermediates. Thus the rates and regioselectivities of metabolism and thus possibly the toxicity and carcinogenicity of DCBs are dependent on the cytochrome P-450 isozymes induced. (Author abstract) (42 Refs)

BENZENE DERIVATIVES

43. BENZENE LEUKEMIA (MEETING ABSTRACT).

Braier L
Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel
Sixth Meeting of the International Society of Haematology, European and African Division, August 30 September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

Benzene (C6H6) is the only industrial chemical possessing aplastic antileukemic and leukemogenic properties in man. Toluene has no myelotoxic action in animals or in man. Other myelodepressive drugs, ie alkylating chemicals are also potentially leukemogenic in man. Acute myeloid leukemia (AML) and erythroleukemia represent the more typical examples of benzene leukemia. They show some features in common: (a) development after many yr of exposure and, in some cases, many mo after the last contact with benzene vapors; (b) leukopenia or only moderate degree of leukocytosis; (c) splenohepatomegaly discrete or absent and (d) unresponsiveness to treatment. A number of cases reported as aplastic anemia in the past might have been examples of acute leukemia with cryptoleukemia features. Hypo-aplastic anemia is frequently found among the antecedents of benzene induced leukemia. The relevance of benzene as an etiological agent for human leukemia (and lymphoma) can be clarified by carrying out a wide prospective survey on all the cases diagnosed in adults, including (a) a careful anamnesis regarding benzene exposure and (b) determination of benzene in blood and/or bone marrow specimens by gas chromatography techniques. A treatment based on the oral administration of large doses of 'antibenzene' compounds, including (1) methyl-donors much as choline, betaine and methionine; (2) thiol-aminoacids such as cysteine-HCl and l-methionine is proposed here for the treatment of all kinds of benzene hemopathy and the prevention of benzene leukemia in so-called 'preleukemic states' resulting from chronic benzene exposure. Prevention of benzene hemopathy can be achieved by (1) prohibiting the manufacture and use of consumer products (ie solvents, cleaning, 'benzines' and adhesives) containing 1% or more pure benzene; (2) lowering the concentration of benzene at the workplace air to 5 ppm or less and (3) avoiding as possible the use of benzene as a reagent for research and teaching purposes. (no Refs)

44. EFFECT OF THE SUSPECTED TUMOR PROMOTERS SACCHARIN, CYCLAMATE, AND PHENOL ON NERVE GROWTH FACTOR BINDING AND RESPONSE IN CULTURED EMBRYONIC CHICK GANGLIA.

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Cancer Res; 42(2):429-432 1982

The suspected bladder tumor promoters saccharin and cyclamate reversibly inhibited nerve growth factor-induced neurite outgrowth in embryonic chick sensory ganglia, and active concentrations of these artificial sweeteners inhibited binding of 125I-labeled mouse submaxillary gland nerve growth factor as well. The skin tumor promoter phenol also reversibly inhibited neurite outgrowth, while comparable concentrations of the nonpromoting but structurally related compounds benzene and fluorobenzene did not. However, in contrast to findings with saccharin and cyclamate, phenol had little, it any, effect on binding of radioactive nerve growth factors. (Author abstract) (58 Refs)

45. TESTS FOR MUTAGENICITY IN SALMONELLA AND COVALENT BINDING TO DNA AND PROTEIN IN THE RAT OF THE RIOT CONTROL AGENT O-CHLOROBENZYLIDENE MALONONITRILE (CS).

von Daniken A, Friederich U, Lutz WK, Schlatter C
Inst. Toxicology, Swiss Federal Inst. Technology, CH-8603 Schwerzenbach, Switzerland
Arch Toxicol; 49(1):15-27 1981

The aim of this study was to determine whether o-chlorobenzylidene malononitrile (CS) exhibits any genotoxic activity towards Salmonella or mammalian DNA in vivo. CS was synthesized with a [14C]-label at the benzylic carbon atom. It was administered ip at a dose level of 13 mg/kg (1 mCi/kg) to young adult male rats. Liver and kidney DNA was isolated after 8, 25, and 75 hr. The radioactivity was at (liver, 8 and 75 hr) or below (all other samples) the limit of detection of 3 dpm. Therefore, a possible binding of CS to DNA is at least 10(5) times lower than that of the strong hepatocarcinogen aflatoxin B1, and 4,000x lower than that of vinyl chloride. In contrast to this lack of DNA binding, but in agreement with the chemical reactivity of CS, a binding to nuclear proteins could be detected with specific activities ranging between 50 and 121 dpm/mg for liver and between 3 and 41 dpm/mg for kidney. Protein binding could well be responsible for its pronounced cytotoxic effects. CS was also tested in the Ames Salmonella/microsome assay. Strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100 were used with or without pre-incubation. Only with strain TA 100 and only without pre-incubation, a doubling of the number of revertants was detectable at the highest dose levels used, 1,000 and 2,000 ug CS per plate. With pre-incubation of TA 100 with CS, a slight increase of the number of revertants was seen at 100 and 500 ug per plate, and a subsequent fall below control values at 1,000 ug. A check for the number of surviving bacteria revealed a strong bacteriotoxicity of the higher doses of CS so that the calculated mutation frequencies, ie, the number of revertants per number of surviving bacteria, increased with doses up to 500 ug. This toxicity could be counteracted in part by the addition of increasing amounts of rat liver microsomes. In the view of these results, and taking into account the rare and low exposure of man, it is concluded that CS will not create a risk for the induction of point mutations or of carcinogenic processes mediated by DNA binding. (Author abstract) (26 Refs)

DRUGS, COSMETICS, DETERGENTS AND OTHER COMMERCIAL MATERIALS

46. ETHYL NITRITE: THE IN VIVO SYNTHESIS OF A MUTAGENIC SUBSTANCE FROM TOBACCO SMOKE AND ETHANOL.

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Fairfield Univ., Fairfield, CT, 06430
Acta Chem Scand [B]; 35(7):485-487 1981

The possibility that nitrogen oxides produced at the temperature of burning tobacco (approx 800 degrees C) react with ethanol vapor in the human body to yield ethyl nitrite (EN) was investigated. Two volunteers ingested 60 ml of 40% (vol/vol) alcohol in water under varying conditions of tobacco smoke. EN levels in breath samples monitored by gas chromatography were undetectable (less than 1.6 picogram (pg)/500 ul) prior to only drinking, only smoking, or after only one of them. EN concentrations were elevated after one drink followed by holding smoke in the mouth for 1-10 sec (65-108 pg/500 ul), and after keeping alcohol and smoke in the mouth for 10 sec (143 and 273 pg/500 ul). Individual degree and manner of smoking and drinking affected the EN concentration in the breath. For up to 5 min after subjects had one drink followed by smoking one cigarette EN was still detectable (7 and 29 pg/500 ul). In vivo production of EN as found in the present study may explain some of the reported synergistic carcinogenesis of tobacco and alcohol. (9 Refs)

47. CHARACTERIZATION, BIOLOGIC ACTIVITY AND MUTAGENICITY OF PROTEIN FROM CIGARETTE TOBACCO, SMOKE AND PIPE CONDENSATE (MEETING ABSTRACT).

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Swinburne Institute of Technology, Hawthorn, Victoria, Australia
Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

The proteins of several extracts of tobacco, smoke and smoke condensate, were examined by mol wt, isoelectric point, (pI), presence of subunits, mutation and immunogenecity. Total protein levels were determined by the Lowry method. The non-protein components were removed by dialysis and ultra-filtration. Hplc, (High pressure liquid chromatography), using TSK3000 SW column (Beckman), resolved high and low mol wt proteins. The solvent system used was 0.2M Na2SO4, 0.01M Na-PO4 buffer pH 6.5, the flow rate was 0.5-1.0 ml/min. The linear relationship between elution vol and mol wt of standard globular proteins allowed determination of mol wt. Up to 12 different proteins were identified by SDS-PAGE (sodium dodecyl sulfate - polyacrylamide gel electrophoresis and mercaptoethanol, which ranged between 20,000-150,000 daltons. This separation had the advantages of mol wt determination and the possible fractionation of the highest mol wt protein into its smaller subunits. When the highest mol wt band (150,000) was reapplied to a fresh SDS-PAGE, two bands were obtained of MW 150,000 and 85,000: when the latter band alone was applied to SDS-PAGE, both hands again appeared, suggesting the existence of aggregates. Dh skin activity was confined to these larger MW bands. Isoelectric focusing was performed using LKB Ampholine pH 3-11 PAGE gels. The focusing pattern demonstrated pI values (4.3-5.8) and the ampholyte mixture exhibited a linear pH profile. The Salmonella/mammalian-microsome mutagenicity test (Ames Assay-TA98 and TA100) with and without metabolic activation was applied to protein fractions obtained from tobacco, smoke and pipe smoke condensate, and significant mutagenic activity was detected. (no Refs)

48. CHARACTERIZATION OF A LYMPHOMA INDUCED BY BUSULFAN AND CHLORAMPHENICOL IN CAF1 MICE (MEETING ABSTRACT).

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Tenth Annual Meeting, Midwest Autumn Immunology Conference, Oct 18-20, 1981, Minneapolis, Minnesota University of Minnesota; 1981

We previously showed that injection of Busulfan and chloramphenicol into CAF1 mice induced the development of T-cell lymphoma in 50% of the mice. The lymphoma cells from the spleen were transplantable into other normal CAF1 mice by intravenous, intraperitoneal, or sc injection. In the recipients the lymhoma cells infiltrated spleen, thymus, and lymph nodes. The sc injection of the cells resulted in subcutaneous nodules with late infiltration of the spleen. The cells from the nodules expressed Thy 1.2 alloantigen and brain associated antigen. None of the Lyt antigens (Lyt 1.1, 1.2 or 2.2) were expressed on the lymphoma cells. The primary sheep cell immune responses of these lymphoma mice were found to be normal. These studies indicate that the lymphoma induced by Busulfan and chloramphenicol are transformed early T cells. (1 Ref)

49. CARCINOGENICITY OF CARRAGEENAN.

Hopkins J

British Industrial Biological Res. Assoc.

Food Cosmet Toxicol; 19(6):779-781 1981

The carcinogenic potential of the food stabilizer carageenan is discussed. Carrageenan has been identified as a cocarcinogen in studies with rats, enhancing methylnitrosourea-, azoxymethane- and dimethylhydrazine-induced colonic carcinoma. Carageenan may also produce colonic carcinoma when used alone. (no Refs)

50. EFFECT OF VARIOUS ANTIOXIDANTS ON 7,12-DIMETHYLBENZ(A)ANTHRACENE INDUCED CARCINOGENESIS IN HAMSTERS.

Khadzhiolov DKh, Balanski RM
Inst. Oncology, Acad. Medical Sciences, Sofia, Bulgaria
Dokl Bolg Akad Nauk; 34(8):1189-1191 1981

Effect of antioxidants (AO) on the incidence of 7,12-dimethylbenz(a)anthracene (DMBA)-induced rhabdomyoblastomas was studied in Syrian hamsters. The animals received single im injection of DMBA (1 mg/kg); a mixture of AO (vitamin C, vitamin E, and sodium selenite) was given either 20 days before or 4 days after DMBA administration. By the end of the experiment (5 mo after DMBA injection), rhabdomyoblastomas were detected in 100% of the animals treated with DMBA alone and in 84.2% of the animals treated with DMBA + AO. (9 Refs) (In RUS)

51. COMPARISON OF THE FREQUENCIES OF SCES INDUCED BY CHEMICAL MUTAGENS IN BONE-MARROW, SPLEEN AND SPERMATOGONIAL CELLS OF MICE.

Palitti F, Tanzarella C, Cozzi R, Ricordy R, Vitagliano E, Fiore M
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Mutat Res; 103(2):191-195 1982

Dose-effect curves are described for the incidence of sister chromatid exchanges (SCE) in Swiss mouse bone marrow, spleen, and spermatogonial cells previously treated in vivo with chemical mutagens (methyl methanesulfonate [MMS]; mitomycin C [MMC]; cyclophosphamide [CP]; 4-nitroquinoline oxide, [4NQO]; bleomycin [BLE]) to evaluate the relative sensitivity of the cell types to SCE-induction by each mutagen. Spontaneous SCE levels were the same for the three cell types, and SCE levels induced by mutagens were similar in the bone marrow and spleen cells, but were significantly less in spermatogonial cells. Mutagen effects on SCE were concentration-dependent, but not linear, suggesting detoxification by the cells at lower doses, even with MMS, which does not require metabolic activation. CP and MMC were efficient mutagens but 4NQO and BLE were not. Spermatogonial cells were evidently better protected against mutagens than the other cells. The SCE method should allow reliable comparison of mutagen sensitivities between somatic and germinal tissues. (17 Refs)

52. ACUTE LEUKEMIA AND MYELOMA (MEETING ABSTRACT).

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Sixth Meeting of the International Society of Haematology, European and African Division, August 30 September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

We observed an unexpectedly high incidence of acute leukemia (AL) (19.6% at 50 mo) among 364 myeloma patients treated with combinations of melphalan, cyclophosphamide, carmustine (BCNU) and prednisone in a Canadian myeloma trial. Acute leukemia developed in all three treatment groups: 5 in the group treated with melphalan and prednisone, and 10 in the 2 groups treated with 3 alkylating agents and prednisone. The acute leukemia was classified as myeloblastic in 11, monoblastic in 2 and erythroleukemic in 2. Patients developing acute plasma cell leukemia were excluded from this analysis. The question of whether this high incidence of AL is caused by treatment with alkylating agents is easier to ask than to answer. The question cannot be be answered by comparing the incidence of AL in myeloma patients treating with alkylating agents with a historical group treated before alkylating agents were used. The median survival of treated patients is about 30 mo, compared with 7 mo for untreated groups; thus, the period at risk for AL is much greater for treated patients. It is difficult to ascribe the high incidence of AL in myeloma to alkylating agents alone; for if these agents do act as leukemogens, they are much more effective in causing AL in myeloma patients than in those with ovarian cancer or Hodgkin's disease. It appears that the etiology of AL and myeloma are linked in some way that does not involve treatment. This increased incidence of AL in untreated patients with myeloma, macroglobulinemia and benign monoclonal gammopathy supports this view. (no Refs)

53. INTERACTIONS OF A FRAGMENT OF BLEOMYCIN WITH DEOXYRIBODINUCLEOTIDES: NUCLEAR MAGNETIC RESONANCE STUDIES.

Lin SY, Grollman AP
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Biochemistry; 20(26):7589-7598 1981

Proton NMR spectroscopy was used to establish certain geometrical parameters of the complexes formed between N-(3-aminopropyl)-2'-(2-acetamidoethyl)-2,4'-bithiazole 4-carboxamide hydrochloride (BLMF), a fragment of bleomycin, and various deoxyribodinucleotides. All proton resonances in these compounds have been assigned; chemical shifts were recorded as functions of their concentration. In the complex formed between BLMF and pdG-dC, chemical shifts of the bithiazole protons (measured with respect to values extrapolated to infinite dilution) was displaced upfield by 0.4 ppm. Other proton resonances of BLMF was shifted upfield but to a lesser extent. After corrections are made for self-stacking, maximum values for induced chemical shifts of the bithiazole protons are reached at a dinucleotide/BLMF ratio of 2. Coupling sums for dinucleotides (12.5-13.7 Hz) were unchanged following complexation, suggesting that there is no marked change in sugar conformation when BLMF is bound. On the basis of these results and of molecular model building studies, we propose a three-dimensional structure of a BLMF:pdG-dC complex in which the thiazole rings are intercalated in the duplex and stack preferentially on the purines. Projected on the same plane, the horizontal axis connecting the center of both bithiazole rings in this configuration superimposes on the axis connecting the centers of the purine bases. In this complex, both thiazole protons extend into the minor groove and the positively charged terminal amine binds to the negatively charged phosphate group of DNA. (Author abstract) (42 Refs)

54. INHIBITORY EFFECT OF INTERFERON ON MMC INDUCED SISTER CHROMATID EXCHANGES (MEETING ABSTRACT).

Ide T, Maekawa T, Edagawa J, Taniwaki M, Sonoda Y, Misawa S, Abe T, Takino T, Kishida T
Department of Medicine and Department of Microbiology, Kyoto Prefectural University of Medicine, Kyoto, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Effect of human lymphocyte interferon (IF) on the frequency of sister chromatid exchange (SCE) was examined. IF itself showed no increase of SCEs in the human lymphocyte culture. Mitomycin C (MMC) (2x10-8M) induced 11.6 SCEs/cell. In the culture containing 200 u/ml of IF, MMC induced 9.6 SCEs. The control level of SCEs in the IF and MMC free culture was 5.1. Results indicated that IF has a inhibitory effect of MMC induced SCEs in vitro. (no Refs)

55. ANTHRAMYCIN BINDING TO DEOXYRIBONUCLEIC ACID-MITOMYCIN C COMPLEXES. EVIDENCE FOR DRUG-INDUCED DEOXYRIBONUCLEIC ACID CONFORMATIONAL CHANGE AND COOPERATIVITY IN MITOMYCIN C BINDING.

Kaplan DJ, Hurley LH
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Biochemistry; 20(26):7572-7580 1981

Anthramycin and mitomycin C (MC) are two DNA reactive drugs, which bind covalently to GC pairs producing different effects on DNA: anthramycin stiffening and MC distortion. This paper describes experiments in which we have used anthramycin as a probe to sense quantitatively the effects on DNA of MC binding. Saturation binding experiments show that both anthramycin and MC partially inhibit the binding of the other drug to DNA (maximum inhibition by MC and anthramycin, 22.4% and 19.7%, respectively) but by a mechanism other than direct site exclusion. This suggests that MC binds in the major groove of DNA, since anthramycin is known to bind in the minor groove. An abrupt reduction in the binding of anthramycin to DNA-MC complexes occurs between MC binding ratios of 0.030 and 0.035, which parallels and probably results from sudden intensification of a MC-induced DNA conformational change occurring between these binding ratios. Dialysis measurements indicate that anthramycin is very possibly binding at sites distant from MC sites and suggest a clustering of closely bound MC chromophores resulting from possible cooperative binding. S1 nuclease digest experiments demonstrate an initial enhancement of nuclease activity in DNA-MC complexes, the magnitude of which correlates well with the reduction of anthramycin binding, relative to the degree of MC binding. The enhanced nuclease activity in these complexes indicates regions of exposed DNA or helix base distortion which is related to or is the result of conformational change. (Author abstract) (43 Refs)

56. GASTROINTESTINAL (GI) TOXICITY OF CIS-DIAMMINEDICHLOROPLATINUM (II) (CDDP) (MEETING ABSTRACT).

Vermorken JB, Pinedo HM
University Hospital, Free University, Amsterdam, Netherlands
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

CDDP causes severe GI toxicity. Particularly nausea (N) and vomiting (V) may cause patients (pts) to refuse treatment. The impact of various doses and schedules has been difficult to ascertain. We administered CDDP to 45 pts (201 cycles) by various methods of administration and in different schedules and doses. Single doses were given either by rapid (5-15 min) infusions, 2-4 hr infusion or 24 hr infusion. The drug was given in 1) a single low dose (SLD) of less than or equal to mg/m2, 2) a single intermediate dose (SID) of 70-90 mg/m2, or 3) a single high dose (SHD) of greater than or equal to 100 mg/m2. In an additional group low dose was given daily x5 (LDx5) in a dose of 20 mg/m(2)/day, by a 3 hr infusion. N/V was classified as mild moderate or severe. Elevations of liver enzymes were graded following World Health Organization criteria. Serum amylase was abnormal when found above 1.25 x upper limit of normal. DCCP was used as a single agent in 25 pts (89 cycles). N and V occurred in 24.43 cycles with SLD and in 40/46 with SID/SHD. Toxicity was severe in 5/57 cycles with SLD/SID and in 10/28 with SHD. Median time to onset of N/V dropped with increasing doses and shorter infusions. Diarrhea occurred in 22% with SHD and 7% with SLD/SID. Elevations of transaminases were observed in 6/21 cycles with SLD, 8/40 with LDx5 and 12/13 with SHD. With SID in 4/6 with rapid infusions, in 1/7 with 2-4 hr infusions and 1/8 with 24 hr infusions. Elevations reached max levels during the first 5 days (all limited to grade I toxicity) and returned to normal within 9 days after the end of infusion. Alkaline phosphatase remained normal, gamma glutamyl transferase was elevated in one patient (2 cycles). Serum amylase showed a pattern of elevation similar to that of the transaminases. It is concluded, that CDDP induced GI toxicity is dose and schedule dependent. (no Refs)

57. EFFECT OF POST-TREATMENT WITH APHIDICOLIN - A SPECIFIC INHIBITOR OF DNA POLYMERASE ALPHA - ON SISTER-CHROMATID EXCHANGES INDUCED BY ETHYL METHANESULFONATE.

Nishi Y, Hasegawa MM, Inui N, Ikegami S, Yamada MA
Biological Res. Center, Japan Tobacco and Salt Public Corporation, Hatano, Kanagawa 257, Japan
Mutat Res; 103(2):155-159 1982

The effect of post-treatment with aphidicolin (AP) on sister-chromatid exchanges (SCE) induced by ethyl methanesulfonate (EMS) was determined in V79 cells. AP at 200 nanog (ng)/ml is toxic to V79 cells, but about half that amount does not affect survival appreciably; treatment did not affect colony size. In the absence of AP, EMS induced SCE in a linear, dose-dependent manner. With 80 ng/ml AP present during the post-treatment (for 2 rounds of replication) SCE were enhanced (1.8x controls) in groups pretreated with EMS (100-400 ug/ml), but not in controls pretreated with dimethyl sulfoxide. AP at 8 ng/ml during post-treatment caused slight, but not significant, increase in SCE; 800 ng/ml AP prevented cell cycle completion. The presence of AP is thought to have increased the effectiveness of EMS in induction of SCE, rather than to have caused SCE directly, since AP alone was without. (24 Refs)

58. STIMULATION OF DNA SYNTHESIS AND CELL PROLIFERATION IN THE LIVER OF RATS FED A CHOLINE-DEVOID DIET AND THEIR SUPPRESSION BY PHENOBARBITAL.

Abanobi SE, Lombardi B, Shinozuka H
Dept. Pathology, Univ. Pittsburgh Sch. Medicine, Pittsburgh, PA, 15261
Cancer Res; 42(2):412-415 1982

Feeding of a choline-devoid (CD) diet and dietary administration of phenobarbital (PHB) are efficient promoters of liver carcinogenesis in the rat. Furthermore, inclusion of PHB in a CD diet results in a synergistic effect, inasmuch as the promoting action of their combination is greater than the sum of those exerted by either agent alone. To investigate the mechanism(s) of action of the two promoters, liver DNA synthesis and liver cell proliferation were studied in rats fed a CD diet, a choline-supplmented diet, or the same diets to which 0.06% PHB was added. DNA synthesis was determined by [3H]thymidine incorporation into DNA and autoradiography, and cell proliferation was determined by mitosis counts. Feeding the CD diet caused an increase of both DNA synthesis and cell proliferation over those present in rats fed the choline-supplemented diet. Inclusion of PHB in the CD diet, on the other hand, inhibited DNA synthesis and cell proliferation. These results indicate that stimulation of cell proliferation per se may not be a sufficient condition for an agent to act as a promoter of liver carcinogenesis. (Author abstract) (32 Refs)

59. ENHANCEMENT OF HEPATOCARCINOGENESIS BY SEQUENTIAL ADMINISTRATION OF CHEMICALS; SUMMATION VERSUS PROMOTION EFFECTS (MEETING ABSTRACT).

Katayama S, Ohmori T, Williams GM
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Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The enhancement of the effects of a carcinogen by a subsequently administered chemical is routinely regarded as evidence of promotion. On the other hand, as an extension of summation of multiple irreversible alterations produced by the total dose of a carcinogen, Nakahara and others have shown that sequential administration of two different carcinogens will produce a summation effect. Thus, the operational definition of a promoter based solely upon its enhancing effect in a protocol of sequential administration becomes questionable. To examine this problem, we undertook a comparison of the effects of phenobarbital (PB) versus diethylnitrosoamine (DEN) when each was given after 2-acetylaminofluorene (AAF). The effects of PB and DEN were comparable, however DEN exerted a greater enhancing effect on the oncogenic outcome of AAF exposure than PB. (no Refs)

60. APPLICATION OF QUANTITATIVE STEREOLOGY TO THE EVALUATION OF ENZYME-ALTERED FOCI IN RAT LIVER.

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Cancer Res; 42(2):465-472 1982

The mathematical science of quantitative stereology has established relationships for the quantitation of elements in three-dimensional space from observations on two-dimensional planes. This report describes the utilization and importance of such mathematical relationships for the quantitative analysis of focal hepatic lesions in terms relative to the vol of the liver. Three examples are utilized to demonstrate the utility of such calculations in the three-dimensional quantitation of hepatic focal lesions. The first is that of a computer-simulated experiment based on defined hypothetical situations. The simulations demonstrate the applicability of the computations described in this report to the evaluation of two-dimensional data from typical animal experiments. The other two examples are taken from actual experiments and involve the transplantation of hepatic cell populations into the liver of suitably prepared hosts and the quantitation of altered foci produced by initiation with diethylnitrosamine-partial hepatectomy followed by promotion with phenobarbital. These studies clearly demonstrate that the frequency and size of foci intersections viewed on two-dimensional tissue sections do not necessarily reflect the number or size of foci in the three-dimensional tissue. Only by quantitating the number and size of the foci in relation to the three-dimensional vol of the tissue can one determine the validity of the proportionality of data from two-dimensional measurements to the total number of foci per volume of tissue. Such a conclusion has important implications for quantitative studies on hepatocarcinogenesis as well as for the enumeration of premalignant lesions which occur during the natural history of carcinogenesis in any solid tissue. (29 Refs)

61. EXPRESSION OF THE TUMOR ALDEHYDE DEHYDROGENASE PHENOTYPE DURING 2-ACETYLAMINOFLUORENE-INDUCED RAT HEPATOCARCINOGENESIS.

Lindahl R, Evces S, Sheng WL
Biochemistry Program, Univ. Alabama, University, AL, 35486
Cancer Res; 42(2):577-582 1982

In aromatic amine-induced rat hepatomas, the aldehyde dehydrogenase (AIDH) phenotype is qualitatively and quantitatively different from that of normal liver. To identify the mechanism(s) underlying the expression of the tumor-specific AIDHs, we have followed the time course of appearance of the new phenotype during hepatoma formation in Sprague-Dawley rats following brief dietary exposures to 2-acetylaminofluorene (0.02%; 32 days). Tumor promotion by phenobarbital (0.05% in the diet) was also used to compare the effects of a variety of tumor induction protocols on the AIDH phenotype. No change in the AIDH phenotype is detectable by total activity assay, gel electrophoresis, isoelectric focusing, or immunochemical methods during or following exposure to carcinogen or promoter until tumors are grossly observed in liver. Concomitant with tumor appearance, the tumor-specific AIDH phenotype appears. The phenotypic change is limited to the tumor; morphologically and histologically normal liver directly adjacent to the tumor and normal lobes of a tumor-bearing liver do not possess the tumor AIDH phenotype. No correlation exists between tumor size and the degree of deviation of the AIDH phenotype from normal. Nor is there any correlation between the degree of AIDH phenotype deviation and the histology of the various tumors observed. We conclude that the tumor-specific AIDH phenotype is not associated with altered liver metabolism due directly to carcinogen or promoter exposure. Rather, the mechanism of this phenotypic change requires that transformation-associated, stable genetic changes occur in the cells affected by carcinogen that are later expressed as the altered AIDH phenotype. (Author abstract) (22 Refs)

62. DISPOSITION OF THE FLAME RETARDANT, TRIS(1,3-DICHLORO-2-PROPYL) PHOSPHATE, IN THE RAT.

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Drug Metab Dispos; 9(5):434-441 1981

Distribution, metabolism, and excretion of tris(1,3-dichloro-2-propyl)phosphate (TDCP) were examined in male Sprague-Dawley rats. Five days after iv administration of 14C-TDCP, 54%, 22%, and 16% of the administered radiolabel was found in the urine, expired air, and feces, respectively; 4% was recovered in the body. TDCP was metabolized to bis(1,3-dichloro-2-propyl)phosphate (BDCP), which was the major urinary, fecal, and biliary metabolite. Other metabolites included 1,3-dichloro-2-propyl phosphate and 1,3-dichloro-2-propanol. TDCP was rapidly distributed out of plasma and into tissues. Less than 19% of administered TDCP was recovered as TDCP in the body 30 min after dosing. Rapid disappearance of TDCP was not due to excretion, as 82% of the administered radiolabel remained in the body and only traces (less than 0.1%) of the administered dose were found in the urine and feces as TDCP 30 min after dosing. Metabolism to BDCP was the major route of elimination of TDCP, whereas BDCP was eliminated primarily by excretion, with 63% of the administered phosphate (TDCP) recovered as BDCP in the urine and feces. 1,3-Dichloro-2-propanol was mutagenic in Salmonella typhimurium TA100 without metabolic activation. TDCP was weakly mutagenic following activation with mouse phenobarbital-induced liver homogenates. Analysis of mutagenicity data on the basis of the number of revertants/umole demonstrated that TDCP was 3-20x more potent than 1,3-dichloro-2-propanol, suggesting that a metabolite other than the alcohol may be responsible for TDCP mutagenicity. Under the same conditions, BDCP and 1,3-dichloro-2-propyl phosphate were not mutagenic. (22 Refs)

63. INDUCTION OF SISTER-CHROMATID EXCHANGE IN HUMAN LYMPHOCYTES BY SMOKE CONDENSATES FROM DIFFERENT BRANDS OF CIGARETTE.

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Mutat Res; 103(2):149-153 1982

The mutagenic activities of smoke condensates (SC) from six commercially available cigarette brands were evaluated by sister-chromatid exchange (SCE) analysis of cultured human lymphocytes. Extracts of SC dissolved in dimethyl sulfoxide (DMSO; 25 mg tar/ml) were added to cultures to yield final concentrations of 50, 100, and 200 ul/ml of culture, and matching controls with DMSO were included. All six SC induced SCE; the highest concentration inhibited cell division in all samples. Results suggest that the amount of tar in cigarettes and the number of cigarettes smoked may affect the mutagenic potency of the resulting SC. (13 Refs)

64. CARCINOGENICITY OF TRICHLOROMETHINE HYDROCHLORIDE (TS-160 SPOFA) AND MORPHOLOGICAL DAMAGE AFTER ITS INTRAAMNIOTIC INJECTION.

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Neoplasma; 28(5):565-574 1981

The cytostatic TS-160 (trichloromethine hydrochloride, tris-/2-chloroethyl/amine hydrochloride) was injected subcutaneously into SPF Wistar rats of both sexes. After all doses used, spindle-cell or even polymorphocellular sarcomas developed at the injection sites in both sexes; after the dose of 0.1 mg/kg daily for 6 months, in 70%; after 0.25 mg/kg, in 79%; and after 1.0 mg/kg weekly for 6 months, in 45% of the rats. Besides, in 21% of the rats receiving the dosage of 0.25 mg/kg mucus-secreting intestinal adenocarcinomas were found. A relationship was apparent between the incidence figures of subcutaneous tumors on the one hand and the daily injection of the low dose versus the intermittent injection of the dose higher by a decimal order on the other hand. In a concurrent test, TS-160 was given to rats in intraamniotic injection on day 18 of pregnancy in doses of 1, 2.5, and 5 ug per embryo. On the first postnatal days, in the affected young rats there were observed morphogenetic disturbances: splanchnocrania and juvenile hair alopecia. These changes became repaired in the further course of postnatal development. (Author abstract) (22 Refs)

REVIEWS AND OTHER COMPOUNDS

65. EFFECTS OF OXYGEN AND SULPHYDRYL-CONTAINING COMPOUNDS ON IRRADIATED TRANSFORMING DNA. PART I. ACTIONS OF DITHIOTHREITOL.

Held KD, Harrop HA, Michael BD
Dept. Therapeutic Radiology, Mayo Clinic, Rochester, MN, 55901
Int J Radiat Biol; 40(6):613-622 1981

The actions and interactions of oxygen and the sulfhydryl-containing compound dithiothreitol (DTT) upon the radiation sensitivity of the biological activity of purified Bacillus subtilis transforming DNA have been examined. It has previously been shown that the sensitivity of transforming DNA irradiated in dilute solution is less when irradiation is performed in 100% O2 than when in 100% N2, ie O2 protects transforming DNA with a dose-modifying factor of about 0.7. DTT protects transforming DNA in a manner that is dependent on DTT concentration and on gassing conditions. In O2 the DTT protection can largely be attributed to the scavenging of-0H radicals by the DTT, but in anoxia DTT exerts a further protective effect which results in an increasing oxygen enhancement ratio (oer) with increasing DTT concentration to a max oer of about 14 at 2-5 mM DTT. This additional protective effect of DTT is attributable to hydrogen atom donation from DTT to DNA radicals, thus chemically repairing the DNA. Oxygen appears to block this chemical repair reaction. (Author abstract) (23 Refs)

66. BONE MARROW KARYOTYPE IN RELATION TO PROGNOSIS AND EXPOSURE TO LEUKAEMOGENIC AGENTS IN PATIENTS WITH ACUTE NONLYMPHOCYTIC LEUKAEMIA (ANLL) (MEETING ABSTRACT).

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Department of Clinical Genetics, Internal Medicine and Oncolicine, University of Lund, Lund, Sweden
Sixth Meeting of the International Society of Haematology, European and African Division, August 30-September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

Chromosome banding pattern of bone marrow cells, cell morphology according to the FAB classification, and clinical findings were compared in two groups of adult patients with ANLL: 52 patients occupationally exposed to chemical solvents, insecticides, or petrol products, and 110 patients with no history of such exposure. Striking differences were found between the two groups: 1) clonal chromosomal aberrations were present in 75% of exposed patients compared with only 32% in the nonexposed group. This relationship was evident in both females and males. 2) 92% of patients exposed to solvents and insecticides had abnormal chromosomes, whereas only 29% of patients exposed to petrol products showed abnormalities. 3) The incidence of certain characteristic karyotypic abnormalities, ie-5/5q-,-7/7q-, +8, +21 and t(8;21) were decidedly more common in exposed than in nonexposed patients. At least one of these changes was present in 92% of exposed patients with aberrations, whereas in the nonexposed group the incidence was only 60%. 4) The monocytic varieties of ANLL were more common in the nonexposed patients, whereas erythroleukemia was more common in the exposed group. 5) There was no difference in survival time between exposed and nonexposed patients and the same correlation was obvious in both groups; patients who had only abnormal metaphases had poorer prognosis than those with only normal bone marrow metaphases (6 vs 1.5 mo). This correlation was obvious in patients classified as AML as well as in the monocytic varieties of ANLL. (no Refs)

67. THE MUTAGENICITY OF DIALKYLAMINOALKYL CHLORIDES IN A BATTERY OF SHORT-TERM ASSAYS.

Thompson CZ, Rinzel SM, Probst GS, McMahon RE
Lilly Res. Laboratories, 307 E. McCarty St., Indianapolis, IN, 46285
Environ Mutagen; 3(1):33-43 1981

A battery of four short-term tests was employed in the study of dialkylaminoalkyl chlorides (DAAC). All DAAC compounds were screened by the concentration gradient technique for their ability to produce an increase in revertants in any of 10 bacterial strains used in the assay. The concentration gradient results were supplemented by determination of concentration-response relationships (Ames test) in the appropriate tester strains. Two additional tests performed were for chemically induced DNA repair in rat hepatocyte primary cultures (HPC-DNA repair) and for mutation at the thymidine kinase locus in the L5178Y mouse lymphoma cell. There was good correlation between results of the gradient plate test and the Ames test. DAAC were active in all test systems. Relative mutagenic potencies of the ethyl chlorides were similar in the bacterial tests and the L5178Y cell assay. Dialkylaminopropyl chlorides (DAAP) were weakly mutagenic in two Salmonella strains but were inactive in other test systems. Results with dialkylaminoethyl compounds suggest that if these agents which can form the aziridinium ion were evaluated in in vivo tests some would be found to be carcinogenic. Data on DAAP indicate that they have a low carcinogenic potential. (9 Refs)

68. THE CHLORINATION QUESTION: HIGHLIGHTS OF THE RECENT CONFERENCE IN CALIFORNIA.

Hileman B
No affiliation given
Environ Sci Technol; 16(1):15A-18A 1982

Health problems associated with water chlorination, including alternative water disinfectants, epidemiological and carcinogenicity studies, cost benefit analysis, the chemistry of chlorination, and effects on aquatic ecosystems are discussed. Alternative disinfectants include chlorine dioxide (ClO2), ozone, and chloramines. ClO2 forms few chlorinated products. One disadvantage is production of the toxic chlorite ion which may possess antithyroid activity. Chloramines are thought to be mutagenic; ozone is expensive and short lived in water systems. Toxicological effects of chlorine have not been carefully studied, even though chlorine byproducts such as trihalomethanes, chlorinated phenols, and haloacetonitriles are possible carcinogens or mutagens. One study suggests a causal relationship between chlorinated drinking water and rectal, bladder, and colon cancer. A new method for measurement of residual halogens, which can detect less than 1 ppb, will allow closer monitoring of water supplies. Organic materials in natural waters are responsible for most of the observed reactions of chlorine with surface waters. Widespread use of chlorine as a water and food disinfectant warrants continued research into its beneficial and harmful effects. (no Refs)

69. MAMMARY CARCINOMA INDUCED BY ORAL ADMINISTRATION OF ETHYL METHANESULPHONATE. DETERMINATION OF SOME OF THE PARAMETERS AFFECTING TUMOR INDUCTION.

Ueo H, Takaki R, Yamagami H, Sugimachi K
Johns Hopkins Univ., Sch. Hygiene and Public Health, 615 North Wolfe St., Baltimore, MD, 21205
Carcinogenesis; 2(12):1223-1228 1981

The carcinogenic activity of ethyl methanesulfonate (EMS), an alkylating agent and a potent mutagen, was examined in Wistar King A and Sprague Dawley rats following oral administration. In the Wistar King A rats, mammary carcinomas were detected in all of the young female rats by the 32nd wk after initiation of the experiment. To determine the optimal experimental conditions for the rapid and invariable induction of mammary carcinomas, the relationship among age, sex, strain of the rats and concentration and duration of EMS administration, and tumor production was investigated. The tumor incidence was higher in the younger female rats and the Wistar rats were more susceptible than Sprague-Dawley rats. Mammary carcinomas were also induced in the younger male rats. In addition, concomitant production of renal tumors occurred by the 40th wk in young rats administered 10(-2) M or 2 x 10(-2) M of EMS soln, while renal and uterine tumors developed concomitantly in the older female rats given 3 x 10(-3) EMS by the 56th wk. Histologically, the prevailing features of tumors were infiltrating ductal adenocarcinoma in the mammary glands, mesenchymal tumor in the kidney, and leiomyosarcoma in the uterus. Methyl methanesulfonate, an analogue of EMS, did not induce tumors in any organs. (Author abstract) (7 Refs)

70. EMERGENCE OF HAMSTER FIBROBLAST TUMORS IN NUDE MICE - EVIDENCE FOR IN VITRO SELECTION LEADING TO LOSS OF GROWTH FACTOR REQUIREMENT.

Perez-Rodriguez R, Chambard JC, Van Obberghen-Schilling E, Franchi A, Pouyssegur J

Centre de Biochimie - CNRS, Universite de Nice, Parc Valrose, 06034 Nice, France

J Cell Physiol; 109(3):387-396 1981

Chinese hamster lung fibroblasts (line CC139) obtained from tumors, were established in vitro, and exponentially growing cultures subjected to mutagenesis by a stock of ethyl methane sulfonate (0.3 ul/ml of complete medium) for 16 hr. After 5-6 generations, selection for colony formation in soft agarose was attempted. Tumorigenesis in nude mice and DNA synthesis in serum-free medium were evaluated for 15 anchorage-independent colonies selected. All of the clones but one had lost both the high anchorage and high serum dependence characteristic of the original CC139 fibroblast line. Partial loss of serum growth factor requirement acquired in vivo seems to be an essential malignant character for bypassing the hormonal growth restraints imposed by the host upon the CC139 cells. (30 Refs)

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1. ETHYLENE OXIDE (ETO): EVIDENCE OF CARCINOGENICITY.
Coene RF
National Inst. for Occupational Safety and Health, Cincinnati, OH
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2. NUTRITIONAL ASPECTS OF CANCER PREVENTION: AN OVERVIEW.
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American Health Foundation, Naylor Dana Inst Disease Prevention, Valhalla, NY, 10595
J Am Vet Med Assoc; 179(12):1404-1409 1981

3. FORMATION OF N-NITROSO COMPOUNDS IN FOODS.
Gray JI
Dept. Food Science and Human Nutrition, Michigan State Univ., East Lansing, MI, 48824
ACS Symp Ser; 174():165-180 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

4. LYMPHOMAS AND LEUKAEMIAS. PART 2: TROPICAL AMERICA.
Jimenez E
Hospital Nacional de Ninos 'Dr. Carlos Saenz Herrera', Apartado 1654, San Jose, Costa Rica
Clin Haematol; 10(3):894-915 1981

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CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

8. THE NATURAL HISTORY OF CARCINOGENESIS: IMPLICATIONS OF EXPERIMENTAL CARCINOGENESIS IN THE GENESIS OF HUMAN CANCER.
Pitot HC, Goldsworthy T, Moran S
McArdle Lab. for Cancer Res., Dept. Oncology, Medical Sch., Univ. Wisconsin, Madison, WI, 53706
J Supramol Struct Cell Biochem; 17(2):133-146 1981

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10. BURKITT'S LYMPHOMA.
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11. PRIMARY HEPATIC CARCINOMA.
Iosquin CJ
Catedra de Medicina Interna A, Facultad de Ciencas Medicas, La Plata, Argentina
Rev Fac Cienc Med La Plata; 4(2):27-31 1981
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12. MUTAGENESIS AND CARCINOGENESIS TESTING IN VITRO.
Casto BC
Northrop Services, Incorporated, P.O. Box 12313, Research Triangle Park, NC, 27709
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OTHER REVIEWS IN CARCINOGENESIS

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Saxen E
Suomen Syoparekisteri, Liisankatu 21 B, 00170 Helsinki 17, Finland
Duodecim; 97(20):1708-1716 1981
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JULY, 1982

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HYDRAZINES AND RELATED COMPOUNDS

1. STUDIES ON EXPERIMENTAL COLON TUMORIGENESIS IN RATS 1. STRAIN DIFFERENCES IN INCIDENCE, LOCATION AND TUMOR TYPES OF 1,2-DIMETHYLHYDRAZINE-INDUCED TUMORS.

Naito Y

Res. Inst. for Nuclear Medicine and Biology, Hiroshima Univ., Hiroshima, Japan

Hiroshima J Med Sci; 30(4):355-362 1981

Susceptibility to 1,2-dimethylhydrazine (DMH), a direct acting carcinogen, in rats with a family history of spontaneous colon tumors (WF/O rats) and in Long Evans (LE) rats was investigated. WF/O and LE rats were divided into a treated group who received 20 mg/kg DMH for 20 wk, and a non-treated control group. Tumorous and non-tumorous sections of the gastrointestinal tract were examined following sacrifice at 10, 15, 20, and 25 wk. Wt gain in treated groups of WF/O and LE rats was similar, however animals with intestinal tumors showed a marked wt loss, diarrhea, or abdominal distension regardless of strains or sexes. Crude colon tumor incidence in WF/O and LE rats was 17/25 and 21/21, respectively. The av number of tumors per rat in WF/O and LE strains were 2.5 and 6.1, respectively. Both crude incidence and the av number of tumors/rat were higher in males than in females. Histologic examination revealed a higher number of colon adenomas in LE rats (41/128 tumors) than WF/O rats (6/42 tumors). Colon carcinoma incidence was higher in WF/O rats (35/42 tumors) than in LE rats (62/128 tumors). LE rats had the majority of tumors (59/128) in the descending colon, while WF/O rat tumors occurred primarily in the ascending colon (19/42). Seven cases of metastases from poorly differentiated adenocarcinomas was found in 18 WF/O rats. Seven cases of metastases (5 from poorly differentiated adenocarcinomas) were found in 21 LE rats. Contrary to expectation, this investigation has shown that WF/O rats were less susceptible to DMH than LE rats. (30 Refs)

2. THE INFLUENCE OF ANDROGENS, ANTI-ANDROGENS, AND CASTRATION ON CELL PROLIFERATION IN THE JEJUNAL AND COLONIC CRYPT EPITHELIA, AND IN DIMETHYLHYDRAZINE-INDUCED ADENOCARCINOMA OF RAT COLON.

Tutton PJ, Barkla DH

Dept. Anatomy, Monash Univ., Clayton, 3168, Australia

Virchows Arch [Cell Pathol]; 38(3):351-355 1982

Androgenic hormones have previously been shown to promote cell proliferation in the small intestine of rat and androgen receptors have been demonstrated in carcinomata of the large intestine of rat. In this study the influence of testosterone and of castration on epithelial cell proliferation in the small intestine, the large intestine and in dimethylhydrazine-induced colonic tumors is compared. Cell proliferation in the small intestine and in colonic tumors was accelerated by testosterone treatment, and cell proliferation in colonic tumors, but not in the small intestine, was retarded following castration. Cell proliferation in colonic tumors was also inhibited by the anti-androgenic drug, Flutamide. Testosterone and castration each failed to influence cell proliferation in the colonic crypt epithelium of both normal and carcinogen-treated animals. (Author abstract) (22 Refs)

3. ENZYMES OF NORMAL, PREMALIGNANT, AND MALIGNANT COLONIC CELLS.

Balis ME, Higgins PJ, Salser JS, Stemmerman GN, Magee PN, Wattenberg LW

Dept. Cell Metabolism and Cell Biochemistry, Memorial Sloan-Kettering Cancer Cen ter, New York, NY, 10021

Banbury Rep; 7:129-139 1981

The villus and crypt cells of rat small intestine contained two different forms of adenosine deaminase (AD) and adenine phosphoribosyltransferase (APRT). The APRTs of normal and neoplastic rat colonic mucosa showed similar properties. Normal colonic mucosa showed predominantly one form of AD, but colonic tumors induced by methylazoxymethanol showed two distinct forms. The ADs of human colonic mucosa and colonic cancer were also distinctive. The tumor AD was smaller than that of normal tissue and was also immunologically distinct. In rat colon, ornithine decarboxylase (ODC) activity was about the same as in liver and only 1-2% that of the small intestine. Carcinogens caused a marked increase in the ODC activity of the target tissue: acetylaminofluorene in the liver, and dimethylhydrazine (DMH) in the colon. Thymidine kinase (TK) activity of the intestine was much higher in the fetal rat than in young or mature rats. After the administration of a colonic carcinogen (DMH), the colonic TK activity increased to levels resembling the fetal TK activity. Assays using rabbit antisera demonstrated two types of TK in normal human intestine, representing the flat mucosa and the crypts. A rabbit antibody against TK from human term placenta cross-reacted against cells from a number of tumor types, including abnormal cervical cells in Papanicolaou smears and colon carcinoma cells. This antibody also reacted with skin fibroblasts from patients with familial colonic polyposis. The specificity of the TK antibody for a variety of tumor types was greatly reduced by preabsorbing the rabbit antiserum with normal human colon extracts. (11 Refs)

4. TUMORIGENESIS WITH 1,1-DIALLYLHYDRAZINE IN MICE.

Toth B, Nagel D, Raha C

Eppley Inst. for Res. in Cancer, Univ. Nebraska Medical Center, Omaha, NE, 68105

Anticancer Res; 1(5):259-262 1981

The carcinogenicity of 1,1-diallylhydrazine (DAH) given to Swiss albino mice in drinking water for life was investigated. Fifty female and 50 male 6-wk-old mice received DAH in drinking water as a 0.03125% soln (av daily intake of DAH was 2.0 mg for females and 2.35 mg for males). Controls were 100 male and 100 female mice given tap water. Treatment reduced survival of both sexes when compared with controls. Lung tumors developed in 38 (76%) treated females and 38 (76%) treated males, and in 25 (25%) untreated females and 26 (26%) untreated males. Forestomach tumors developed in 7 (14%) treated females and 17 (34%) treated males, and in 4 (4%) untreated females. Histopathologically, the lung tumors were adenomas and adenocarcinomas and the forestomach tumors were squamous cell papillomas and carcinomas. The relative carcinogenic potencies of other disubstituted allylhydrazines are discussed. The tumorigenic potency of these co mpounds was strongly dependent on the nature of the alkyl substituents. (26 Refs)

5. SOMATIC MUTATIONS INDUCED BY MALEIC HYDRAZIDE AND ITS POTASSIUM AND DIETHANOLAMINE SALTS IN THE TRADESCANTIA MUTATION ASSAY.

Gichner T, Veleminsky J, Pokorny V
Inst. Experimental Botany, 16000 Praha 6, Flemingoro 2, Czechoslovakia
Mutat Res; 103(3-6):289-293 1982

Maleic hydrazide (MH), and its diethanolamine and potassium salts exhibited high mutagenic activity in Tradescantia clone 4430 and clone 02 assays. All three compounds were mutagenic to clone 4430; MH was more effective at inducing mutations in influorescences that stem cuttings. Clone 4430 was markedly more sensitive to mutagens than clone 02, a finding which disagrees with previous results. (14 Refs)

6. REORGANIZATION OF HELA CELL CYTOSKELETON INDUCED BY AN UNCOUPLER OF OXIDATIVE PHOSPHORYLATION.

Maro B, Bornens M
Centre de Cytologie Experimentale du CNRS, 67 rue Maurice Gunsbourg, 94200 Ivry s/Seine, France
Nature; 295(5847):334-336 1982

Effects on the cytoskeleton of impairment of mitochondrial functions induced by three metabolic inhibitors: sodium azide, which inhibits electron transport; oligomycin, which inhibits ATP synthetase; and carbonylcyanide p-trifluoromethoxyphenylhydrazone (FCCP), a proton ionophore which uncouples electron transport from ATP synthesis, were studied. FCCP induced a disruption of HeLa microtubules after 1 hr. After 6 hr treatment, short microtubules were seen regrowing from the juxtanuclear microtubule-organizing centres (MTOC). FCCP had a slower effect on vimentin filaments. The filaments began to aggregate after 1 hr treatment and gathered as perinuclear bundles after 6 hr. The distribution of actin was apparently unchanged. Doses of FCCP used were non-toxic for the cells. Effects of FCCP were absent with doses below 10(-5) M and complete at 3 x 10(-5) M. Similar but weaker effects were provoked by 2,4-dinitrophenol (DNP). MTOC could be easily identified and microtubules disappeared. Loose bundles of vimentin filaments were observed around the nuclei, distributed in a different pattern from that seen in control cells. Oligomycin and sodium azide had no such effects on the cells. Results showed that the effects of FCCP are not provoked by mitochondrial ATP depletion, but cold be linked to another event related to rapid dissipation of the mitochondrial electrochemical gradient. (13 Refs)

HETEROCYCLIC COMPOUNDS

7. US BEGINS TO GET TOUGH ON ETHYLENE OXIDE.

Heneson N
Washington, DC
New Sci; 93(1291):294 1982

Tighter safety controls for ethylene oxide (EO), proposed by the Occupational Safety and Health Administration (OSHA) are discussed. EO, a major industrial chemical, is a suspected human mutagen according to newer, more extensive studies. New OSHA standards would lower the permissible av 8 hr worker exposure to EO, which is currently set at 50 ppm. A petition to OSHA by a lobby group and a labor union to set an emergency standard of 1 ppm averaged over 8 hr was rejected. Several industries, however, have already set a safety standard of 10 ppm of their own volition. (no Refs)

8. AN EVALUATION OF THE GENETIC TOXICITY OF EPICHLORHYDRIN. A REPORT OF AN EXPERT GROUP OF THE INTERNATIONAL COMMISSION FOR PROTECTION AGAINST ENVIRONMENTAL MUTAGENS AND CARCINOGENS.

Sram RJ, Tomatis L, Bridges BA, Clemmesen J
(c/o Lohman), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(3):299-319 1981

Genetic toxicity of epichlorhydrin (ECH) is reviewed. ECH produces gene mutations in various submammalian species, in mice, cultured mouse lymphoma cells, and in a Syrian hamster transplacental mutagenicity assay. Chromosomal damage has been reported in Vicia faba, human peripheral lymphocytes in vitro, rodent bone marrow, germ cells of mice, and in human peripheral lymphocytes and body fluids. ECH produces repairable DNA damage characteristic of an alkylating agent. The International Collaborative Program on Short-term Tests for Carcinogenicity reported that ECH was mutagenic in the in vitro systems, did not induce sex-linked recessive lethal mutations in Drosophila, and induced sister-chromatid exchanges in mammals. Application of ECH to the skin of rats and mice failed to produce tumors. Administration of ECH sc and im (but not ip) to mice produced local sarcomas and adenomas, although results were inconclusive in one study. Inhalation of 100 ppm (but not 10 ppm) of ECH for 30 days in rats induced squamous cell carcinomas in the nasal cavity. Epidemiologic studies of workers exposed to ECH provided no evidence of a carcinogenic effect; no nasal tumors were observed and the increase in lung cancers found could have been attributed to heavy cigarette consumption. Suggestions for further studies are made. (84 Refs)

9. QUANTUM CHEMICAL STUDIES OF AFLATOXINS: METABOLISM AND CARCINOGENIC ACTIVITY.

Loew GH, Poulsen MT
SRI International, Life Sciences Div., Menlo Park, CA, 94025
Int J Quantum Chem Quantum Biol Symp; 8:95-107 1981

Semiempirical all-valence electron molecular orbital methods were used to further determine the extent to which the parent compound susceptibility to epoxidation and the stability of the epoxide and its carbocation play a role in determining the relative carcinogenic and mutagenic potencies of five aflatoxins (aflatoxin B1, aflatoxin G1, aflatoxin P1, aflatoxin M1, aflatoxicol) and two biosynthetic precursors (versacolorin A, sterigmatocystin). Results support the initial experimental findings that these electronic factors do not determine the relative potencies of aflatoxins or their biosynthetic precursors. (33 Refs)

10. PHOTOCHEMICAL EPOXIDATION OF AFLATOXIN B1 AND STERIGMATOCYSTIN: SYNTHESIS OF GUANINE-CONTAINING ADDUCTS.

Buchi G, Fowler KW, Nadzan AM
Dept. Chemistry, Massachusetts Inst. Technology, Cambridge, MA, 02139
J Am Chem Soc; 104(2):544-547 1982

Benzil-sensitized photoepoxidation of the mycotoxins aflatoxin B1 and sterigmatocystin provided the presumed reactive epoxides which have been implicated in mutagenesis and carcinogenesis. These intermediates, after trapping with 3',5'-di-Obutyryldeoxyguanosine and hydrolysis with aqueous acid, led to the N(7)-guanine adducts identical with the in vivo natural products. This method provides an alternative to the more complex procedures of organ perfusion and whole body dosing. (Author abstract) (26 Refs)

11. THE MUTAGENIC POTENTIAL OF 4 NITROPHENYL BIS(2-THIENYL)-PHOSPHINATE; 4-NITROPHENYL 2-FURYL(METHYL)-PHOSPHINATES; 4-CYANOPHENYL BIS(2-FURYL)-PHOSPHINATE; 4-NITROPHENYL BIS(2-FURYL)-PHOSPHINATE.

Sauers LJ, Pulliam FR, Fruin JT

Letterman Army Inst. Res., San Francisco, CA

The Mutagenic Potential of 4 nitrophenyl bis(2-thienyl)-phosphinate; 4-nitrophenyl 2-furyl(methyl)-phosphinates; 4-cyanophenyl bis(2-furyl)-phosphinate; 4-nitrophenyl bis(2-furyl)-phosphinate. Available from National Technical Information Service, Springfield, VA, as ADA105 978/1:, 37 pp., 1981.

The mutagenic potential of 4 nitrophenyl bis(2-thienyl)phosphinate; 4-nitrophenyl 2-furyl(methyl)phosphinate 4 cyanophenyl bis(2-furyl)phosphinate; 4-nitrophenyl bis(2-furyl)phosphinate was assessed by using the Ames Salmonella/Mammalian Microsome Mutagenicity Assay. Tester strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 were exposed to doses ranging from 1 mg/plate to 0.00032 mg/plate. It was determined that none of the tested substances had mutagenic potential. (Author abstract)

INORGANIC AGENTS AND PARTICULATES INCLUDING FIBERS

12. CHARACTERIZATION OF POLYCYCLIC KETONES AND QUINONES IN DIESEL EMISSION PARTICULATES BY GAS CHROMATOGRAPHY/MASS SPECTROMETRY.

Choudhury DR

Vick Div. Res. and Development, Richardson-Vicks Incorporated, 1 Bradford Road, Mount Vernon, NY, 10553

Environ Sci Technol; 16(2):102-106 1982

High-resolution gas chromatography/mass spectrometry was used to determine the chemical composition of two highly mutagenic subfractions of the neutral fraction of a diesel particulate extract. Diesel emission particulates were collected from a Volkswagen Rabbit by the dilution tunnel method and the two subfractions were isolated by silica gel chromatographic fractionation of the neutral extract. Of seven subfractions prepared, subfractions 4 and 5 had the highest specific mutagenicity in the Ames Salmonella mutagenesis assay, with subfraction 4 accounting for 52% of the direct-acting mutagenicity and subfraction 5, 13%. Both direct-acting mutagens and promutagens which required metabolic activation were found in the subfractions. Elution patterns suggested that the subfractions contained compounds more polar than parent and alkyl-substituted polycyclic aromatic hydrocarbons. Ketone, quinone, carboxaldehyde, and hydroxy derivatives and their alkyl homologues were characterized. The single largest family of compounds detected were 9-fluorenone and its C1-C4 alkyl homologues. The mutagenicity of most of the compounds identified is unknown. (18 Refs)

13. DISTRIBUTION OF TRACE METALS IN NUCLEI AND NUCLEOLI OF NORMAL AND REGENERATING RAT LIVER WITH SPECIAL REFERENCE TO THE DIFFERENT BEHAVIOR OF NICKEL AND CHROMIUM.

Ono H, Wada O, Ono T
Dept. Hygiene, Sch. Medicine, Gunma Univ., Maebashi, Gunma 371, Japan
J Toxicol Environ Health; 8(5/6):947-957 1981

Distribution of metals, including Ni and Cr, in relation to the amounts of nucleic acids and proteins in normal and partially hepatectomized rat liver nuclei and nucleoli were investigated. The contents of Ca, Zn, Cu, and Mn in whole cells were much higher than those of Cr and Ni. While little Cr and Ni was found in cells, greater than 20% was found in nuclei. Metal concentrations (except for Cr) in hepatectomized liver nuclei and nucleoli changed synchronously with changes in the amount of nucleic acids and proteins. While the cause of the lack of Cr and Ni synchronization is not known, it may be related to the carcinogenicity of the metals. (49 Refs)

14. PARAMECIUM TETRAURELIA. PRE-SCREEN FOR HAZARDOUS CHEMICALS: A RAPID-DETECTOR SYSTEM FOR HEALTH HAZARDS. PROGRESS REPORT.

Smith-Sonneborn J
Dept. Zoology and Physiology, Wyoming Univ., Laramie, WY
Paramecium Tetraurelia. Pre-Screen for Hazardous Chemicals: A Rapid-Detector System for Health Hazards. Progress Report. Available from National Technical Information Service, Springfield, VA, as DE81025884:, 18 pp., 1981.

Genotoxic and cytotoxic effects of dilutions of oil shale proces waters from three different retorting processes were evaluated using the Paramecium tetraurelia and the Salmonella assays. Process waters from above-ground, true in situ, and modified retorting process were analyzed. Significant mutagenicity was detected in waste water from both the above ground and true in situ retorting processes in both the Salmonella and Paramecium bioassays. The Salmonella assay required the addition of the rat liver S9 fraction; the Paramecium bioassay was more sensitive to genotoxic effects from an above-ground retort water without the addition of the rat liver fraction. Mutagenicity of the dilutions tested from the modified retort process was detected only in the Paramecium system The waste water from the above-ground retort process was the most toxic to both the protozoan and bacteria. Since the chemical composition of oil shale process waters can vary with: (1) the retorting process used, (2) the temperature of the retorting, (3) the composition of the shale rock, and (4) the sampling and storage procedures, the differences in biological activity observed between water can reflect differences in water contamination. (Author abstract)

15. SISTER-CHROMATID EXCHANGES INDUCED BY SOME CHROMIUM COMPOUNDS IN HUMAN LYMPHOCYTES IN VITRO.

Gomez-Arroyo S, Altamirano M, Villalobos-Pietrini
Laboratorio de Citogenetica y Mutagenesis Ambiental, Universidad Nacional Autonoma de Mexico 20, Centro de Ciencias de la Atmosfera, DF, Mexico
Mutat Res; 90(4):425-431 1981

Human lymphocytes were treated with K2Cr2O7 (0.025-0.1 ug/ml),CaCrO4 (0.01-0.02 ug/ml), or CrO3 (0.025-0.1 ug/ml) in the presence of 5-bromodeoxyuridine for two replicative cycles. All three test compounds increased the occurrence of sister chromatid exchanges (SCE) in a dose-dependent manner, as detected by a combination of fluorescent and Giemsa staining methods. Compounds containing Cr++++++ were effective in producing SCE in the order CaCr04 greater than CrO3 greater than K2Cr2O7. (50 Refs)

16. CHROMATE LUNG CANCER WITH SPECIAL REFERENCE TO ITS CELL TYPE AND RELATION TO THE MANUFACTURING PROCESS.

Abe S, Ohsaki Y, Kimura K, Tsuneta Y, Mikami H, Murao M
First Dept. Medicine, Hokkaido Univ., North 14, West 5, Sapporo, Japan
Cancer; 49(4):783-787 1982

The manufacturing process of the chromate industry can be classified into five steps. The main hazardous pollutants of the first step are trivalent chromate compounds, and those of the second and third steps are hexavalent chromate compounds. Analysis of the detailed working history of chromate workers with bronchogenic carcinoma, yielded the following results: the work history of chromate lung cancer patients in the first step, which produced mainly trivalent chromate dust, was rather short. Patients with small cell carcinoma were engaged mainly in the second step (98.1% of the total working months), where they were heavily exposed to hexavalent chromate dusts. Patients with squamous cell carcinoma were engaged rather evenly in the second and fourth steps, and somewhat longer in the third step. Comparisons of the exposure periods revealed that the working history of small cell carcinoma patients was significantly shorter than that of squamous cell carcinoma patients. There were many more heavy smokers among the squamous cell carcinoma group as compared to the small cell carcinoma patients. Based on these results, it is concluded that the cell type of occupational lung cancer was mainly small cell carcinoma when the exposure to carcinogenic agents was heavy, and that the carcinogenicity of chromate was derived mainly from hexavalent chromate rather than trivalent compounds. (Author abstract) (9 Refs)

17. STUDIES ON MUTAGENIC EFFECT OF ENVIRONMENTAL FACTORS IN NONFERROUS METALLURGICAL PLANTS.

Dziekanowska D
Zaklad Biologii Ogolnej, Instytut Biologiczno-Morfologiczny Slaskiej Akademii Medycznej, ul. K. Marksa 19, 41-808 Zabrze, Poland
Patol Pol; 32(2):263-268 1981

Chromosome aberrations in peripheral blood lymphocytes were studied in 32 workers occupationally exposed to nonferrous metals: (15 lead, 11 cadmium, 6 zinc). The numbers of aberrant cells and of structural chromosome aberrations in the workers showed variations from one worker to another, but the mean values showed an increase, compared with nonexposed controls. Especially significant differences were observed in the structural rearrangements (dicentric chromosomes and translocations), as well as disturbances in spiral formations. The frequency of sister chromatid exchanges (SCE) in lymphocytes showed a decrease in the workers compared with controls. This decrease in the workers may be related to the mutational senescence of cells. The results indicate that the synergistic effect of the different metals can induce chromosome mutations under the conditions of long-term exposure in vivo. (no Refs) (In POL)

18. IN VITRO EVALUATION OF CADMIUM-INDUCED AUGMENTATION OF THE ANTIBODY RESPONSE.

Fujimaki H, Murakami M, Kubota K
National Inst. Environmental Studies, Yatabe-machi, Tsukuba Ibaraki 305, Japan
Toxicol Appl Pharmacol; 62(2):288-293 1982

Enhancement of the in vitro primary, plaque-forming cell antigenic response to sheep red blood cells by exposure to 4-40 uM cadmium was investigated in spleen cell cultures from 2-3-mo-old male BALB/c mice. Results showed that augmentation by cadmium exposure is primarily due to the activation of B cells required for antibody response. (13 Refs)

19. FERTILIZATION AND LARVAL DEVELOPMENT IN SEA URCHINS FOLLOWING EXPOSURE OF GAMETES AND EMBRYOS TO CADMIUM.

Pagano G, Esposito A, Giordano GG
Fondazione 'Sen. Pascale', v. M. Semmola, 12, 80131 Napoli, Italy
Arch Environ Contam Toxicol; 11(1):47-55 1982

Gametes and embryos of three species of sea urchins were exposed to cadmium chloride (10(-8) to 10(-3) M). Acute toxic or prolonged subtoxic exposure to Cd++ of either gamete was not embryotoxic. High level exposure of ova promoted fertilization. High level exposure of sperm depressed fertilization while low level exposure elevated it. Acute exposure of cleaving eggs was not mutagenic. Exposure of embryos caused severe abnormalities in, or total suppression of skeletal differentiation, depending on the cadmium level. (22 Refs)

20. ARSENIC-STATE OF THE ART.

Landrigan PJ
Div. Surveillance, Hazard Evaluations, and Field Studies, NIOSH, 4676 Columbia Parkway, Cincinnati, OH, 45226
Am J Ind Med; 2(1):5-14 1981

Occupational and domestic exposure to arsenic in United States of America is briefly reviewed: human elimination mechanisms; assay implications; acute poisoning; subacute and chronic toxicity to the skin (dermatitis, Bowen's disease, basal cell and squamous cell carcinomas), liver (cirrhosis, angiosarcoma), respiratory tract (lung cancer), and nervous (peripheral neuropathy), cardiovascular (acrocyanosis), 'blackfoot disease' (gangrene), myocardial infarction, Reynaud's (phenomenon), and hematopoietic (disturbed erythropoiesis, equivocal cancer) systems. Animal cancer-induction studies remain negative. Mutagenicity/chromosomal aberration studies in bacterial-animal-human systems are touched upon. (50 Refs)

21. DIESEL-EXHAUST-PARTICLE EXTRACT ENHANCEMENT OF CHEMICAL-INDUCED MUTAGENESIS IN CULTURED CHINESE HAMSTER OVARY CELLS: POSSIBLE INTERACTION OF DIESEL EXHAUST WITH ENVIRONMENTAL CARCINOGENS.

Li AP, Royer RE
Inhalation Toxicology Res. Inst., Lovelace Biomedical and Environmental Res. Inst., P. O. Box 5890, Albuquerque, NM
Mutat Res; 103(3-6):349-355 1982

Dichloromethane extracts of exhaust particles (EP) filtered from the exhaust of diesel passenger cars of five different manufacturers were tested in combination with known mutagens using the Chinese hamster ovary (CHO) hypoxanthine-guanine phosphorylase assay. N-Methyl-N'-nitro-N-nitrosoguanidine (MNNG: 0.5 ug/ml) and benzo(a)pyrene [B(a)P: 0.5 ug/ml] were administered with and without diesel EP extract (60 ug/ml in dimethyl sulfoxide) to CHO cells grown with and without Aroclor 1254-induced rat-liver S9 activator. Mutagenicity of the EP extract alone was uniformly low, but treatment of CHO cells with mutagen plus EP extract consistently yielded a mutant frequency higher than expected. Without S9 activation, combined treatment of EP + MNNG gave a mutant frequency 1.4-1.9 x higher than expected. With S9 activation the EP + B(a)P treatments resulted in an observed mutation frequency 2.8-3.2 x the expected value. The observed enhancement phenomenon is highly reproducible, and also affects sister-chromatid exchanges and mutation to ouabain resistance. (21 Refs)

22. MUTAGENICITY OF PARTICULATES IN SMALL ENGINE EXHAUST.

Ohnishi Y, Okazaki H, Wakisaka K, Kinouchi T, Kikuchi T, Furuya K
Dept. Bacteriology, Sch. Medicine, Univ. Tokushima, Tokushima 770, Japan
Mutat Res; 103(3-6):251-256 1982

Mutagenic activities of particulates in filtered exhaust from a small gasoline engine, a small diesel engine, and the new NiCE (Nippon Clean Engine Research Institute) thermo-atmosphere combustion gasoline engine were compared using the Ames test (strains TA98 and TA100; with and without S9). Generally the number of revertants in colonies treated with NiCE engine exhaust extracts was much lower than colonies treated with exhaust extracts of either the traditional gasoline engine or the small diesel engine. With a catalytic muffler emissions from the NiCE engine were markedly less mutagenic; no benzo(a)pyrene emissions were detected by high performance liquid chromatography of the muffled exhaust. (13 Refs)

23. MUTAGENS IN DIESEL EXHAUST PARTICULATE: IDENTIFICATION AND DIRECT ACTIVITIES OF 6-NITROBENZO(A)PYRENE, 9-NITROANTHRACENE, 1-NITROPYRENE AND 5H-PHENANTHRO(4,5-BCD)PYRAN-5-ONE.

Pitts JN, Lokensgard DM, Harger W, Fisher TS, Mejia V, Schuler JJ, Scorziell GM, Katzenstein YA
Statewide Air Pollution Res. Center, Univ. California, Riverside, CA, 92521
Mutat Res; 103(3-6):241-249 1982

Combined chemical/microbiological analyses of diesel exhaust particulate organic matter (POM) are reported. Levels of three nitroarenes 1-nitropyrene (1NP), 9-nitroanthracene (9NA), and 6-nitrobenzo(a)pyrene (6NBP) were determined. A new type of direct mutagen in combustion-generated POM, 5H-phenanthro(4,5-bcd) pyran-5-one (IPAP) had been also determined. The base + neutral/(bn) fractions of dichloromethane (DCM) extracts of diesel exhaust POM were much more mutagenic than the acid fraction in the Ames test with Salmonella strains TA98 and TA98R, and the latter strain, a nitroreductase-deficient isolate of TA98, showed less response, indicating that direct activity of the bn fraction was due to nitro-substituted compounds. The presence of 1NP, 9NA, 6NBP, and IPAP in the bn fraction was confirmed by capillary gas chromatography/mass spectra analysis and other tests. Highly purified samples of the four compounds were compared using the Ames test with the standard mutagens quercetin, 2-nitrofluorene and benzo(a)pyrene, and the other mutagens (1 or 3)-nitrobenzo(a)pyrene and (3 or 1)-nitrobenzo(a)pyrene. 1NP accounted for 20 and 27% of the direct mutagenic activity exhibited by the total DCM extract and bn fraction, respectively. The compound accounts for about 50% of the 'nitroarene' portion of the direct activity, defined here as the difference between TA98 and TA98R responses, whereas 9NA and 6NBP make negligible contributions to the total activity. The activity of the lactone IPAP is reported here for the first time, and UV, fluorescence, and mass spectra data for the compound are given. (47 Refs)

24. URANIUM MINER LUNG CANCER STUDY. PROGRESS REPORT, 1 JULY 1980-1 JULY 1981.

Saccomanno G
Saint Mary's Hosp. and Medical Center, Grand Junction, CO
Uranium Miner Lung Cancer Study. Progress Report, 1 July 1980 - 1 July 1981. Available from National Technical Information Service, Springfield, VA, as DE81030162:, 8 pp., 1981.

The projects supported during the past year consist of: (a) collection of material from uranium miners known to have cancer of the lung into a tumor registry; (b) collection of interesting cases for second edition of the Manual on Pulmonary Cytology; (c) the regression study has been modified by computerization of rereads of all cases which showed moderate atypical squamous cell metaplasia or higher since 1968; (d) continuation of sputum collection, and collection of lungs from decreased miners; (e) cooperation with fluorescent bronchoscopy development for localization of carcinoma in situ of the lung; (f) the immunological studies are presently funded by the Abbott Laboratories, but are closely associated with the lung cancer studies. Our findings suggest that patients developing lung cancer concomitantly develop immune suppression; and (g) a small plastic tube has been developed which will aid in the removal of cells from fiberoptic brushings. The plastic mold is presently being developed by Midi-Tech Corporation in Boston and the tube will be available in September 1981. Analysis of the incidence of small cell cancers of the lung over the last 30 yr indicates that the incidence has dropped to 22% during 1975-1979 whereas it was 76.5% during the 5 yr span from 1954-1959. General observations indicate that cigarette smoking is the most potent carcinogen, but that tumors are increased in miners who smoke. Moreover, the ultimate incidence of oat cell carcinoma results in earlier death than with other tumor types. The most commonly found tumor in the non-smoking miner is the small cell type. (Author abstract)

25. CARCINOGENIC EFFECTS OF RADON DAUGHTERS, URANIUM ORE DUST AND CIGARETTE SMOKE IN BEAGLE DOGS.

Cross FT, Palmer RF, Filipy RE, Dagle GE, Stuart BO
Biology Dept., Pacific Northwest Lab., Richland, WA, 99352
Health Phys; 42(1):33-52 1982

The development of pulmonary lesions in beagle dogs was studied following chronic inhalation exposures to radon (at 105 +-20 nCi/l), radon daughters (at 605 +-169 WL), uranium ore dust (at 12.9 +-6.7 mg/m3) and cigarette smoke. Chronic exposures to mixtures of these agents caused significant lifespan shortening when compared with controls. Survival times of controls and smoke-exposed dogs were equivalent during the 4 to 5-yr mean survival time of the dogs exposed to radon-daughter and ore-dust mixtures (with or without added cigarette smoke). Animals with tumors of the respiratory tract generally had cumulative radon-daughter exposures exceeding 13,000 WLM, and their survival time was longer than the survival time of nontumor-bearing animals. Under the conditions of the experiment, exposure to cigarette smoke was found to have a mitigating effect on radon daughter-induced tumors. It is uncertain whether this would be a general finding applicable to other levels of exposure to radon daughters, uranium ore dust and cigarette smoke. Exposures to smoke from 10 cigarettes/day, 7 days/wk produced no significant respiratory tract lesions. However, exposure to 20 cigarettes/day, 7 days/wk resulted in pulmonary emphysema, fibrosis and chronic bronchitis and bronchiolitis. Emphysema and fibrosis were much more prevalent and severe in the dogs exposed to mixtures which included radon daughters and uranium ore dust. These dogs also had adenomatous lesions which progressed to squamous metaplasia of alveolar epithelium, epidermoid carcinoma and bronchioloalveolar carcinoma. Pathologic changes in the airways of these dogs were most prominent in the nasal mucosa, and included a few squamous carcinomas in the nasal cavity. We conclude that the beagle dog is a useful animal for modeling pulmonary lesions produced by uranium mine air contaminants. Tumors were produced at levels that did not greatly exceed some exposures reported for uranium miners. These tumors, found after approx 50 mo of exposure, might partially account for the absence of tumors in experiments where exposures terminated before 50 mo. (Author abstract) (33 Refs)

26. COMPARATIVE EFFECTS OF FIBROUS AND NONFIBROUS MINERALS ON CELLS AND LIPOSOMES.

Woodworth CD, Mossman BT, Craighead JE
Dept. Pathology, Univ. Vermont, Coll. Medicine, Burlington, VT, 05405
Environ Res; 27(1):190-205 1982

The comparative effects of chrysotile asbestos, silica, talc, kaolinite and montmorillonite on cellular and artificial membranes were examined using three test systems - monolayer cultures of tracheal epithelial cells, suspensions of sheep erythrocytes (RBC), and preparations of phospholipid-cholesterol vesicles. The four minerals caused perturbations in each system, although to varying degrees. Membrane alterations induced by chrysotile asbestos and the clay mineral montmorillonite were more striking than those caused by other dusts. The results obtained with the three test systems were consistent. Electron microscopic observations indicated that the particles were phagocytized by cultured epithelial cells of hamster tracheal origin and developed intimate associations with the RBC plasma membrane. These interactions are discussed with regard to possible mechanisms of cellular injury and their relevance to pulmonary disease. (Author abstract) (36 Refs)

AMIDES, CARBAMATES AND UREAS

27. DNA REPAIR STUDIES ON DIALLATE, TRIALLATE AND SULFALLATE IN HUMAN CELL CULTURES.

Benigni R, Dogliotti E, Falcone E, Calcagnile A
Laboratorio di Tossicologia, Istituto Superiore di Sanita, Roma, Italy
Mutat Res; 103(3):385-390 1982

Induced unscheduled DNA synthesis (UDS) was measured in cells of the EUE line of epithelial-like cells by (3H)thymidine autoradiography and (3H)thymidine/(14C)thymidine incorporation ratio determined after scintillation counting. Autoradiography studies showed that the structurally related carbamates diallate, triallate, and sulfallate caused a significant, dose-dependent increase in UDS over the range of 10(-6) -10(-4) M, with dose-dependent inhibition at 10(-3) and 10(-2) M. No such effect was observed in the 3H/14C assay although treatment with N-methyl-N'-nitro-nitrosoguanidine and methylmethane sulfonate increased (3H)thymidine incorporation. The present results extend to human cells the suggested mutagenicity and carcinogenicity of these pesticides, which had been previously demonstrated in fungal and animal systems. (12 Refs)

28. MUTAGENIC EVALUATIONS OF TWO RUBBER ACCELERATORS.

Hinderer RK, Knickerbocker M, Koschier FJ
(c/o B. F. Goodrich Co.) Environmental Health Dept., 500 South Main St., Akron, OH, 44318
Toxicol Appl Pharmacol; 62(2):335-341 1982

The potential of N-oxydiethylene thiocarbamyl-N-oxydiethylene sulfenamide (OTOS) and N-oxydiethylene-2-benzothiazole sulfenamide (OBTS) to cause dominant lethal mutations in BLU: (SD) BR Sprague-Dawley rats was studied. OTOS (6.25, 1.25, or 25.0 mg/kg/day for 56 days) or OBTS (125, 250, or 500 mg/kg/day for 56 days) administered by gavage to males prior to mating did not produce dominant lethal mutations; only in positive controls given triethylenemelamine (0.25 mg/kg in a single ip dose 1 day before mating) were the number of implantation sites and preimplantation losses significantly decreased and the number of early fetal deaths/pregnant female significantly elevated. (11 Refs)

29. ACUTE EFFECTS OF SELECTED HEPATOTOXIC AGENTS ON POLYRIBOSOMES AND PROTEIN SYNTHESIS IN THE LIVERS OF RATS FED PURIFIED DIETS CONTAINING HEPATOCARCINOGENS.

Sidransky H, Verney E
Dept. Pathology, George Washington Univ. Medical Center, Washington, DC, 20037
Exp Mol Pathol; 36(1):72-85 1982

This investigation was concerned with the effects of certain hepatocarcinogens ingested for long- or short-term intervals upon selected responses of rat liver to specific hepatotoxic stimuli. Rats fed ad libitum for long (3 to 45 wk) periods or force-fed for short (3 days) periods purified diets containing a single hepatocarcinogen, ethionine, N-2-fluorenylacetamide, 3'-methyl-4-dimethylaminoazobenzene, or thioacetamide, were subjected to the acute administration of a single hepatotoxic agent, such as puromycin, actinomycin D, sparsomycin, hypertonic NaCl or CCl4, and hepatic protein synthesis (in vitro) and polyribosomal aggregation were evaluated. Relating to in vitro protein synthesis, in long-term experiments, puromycin induced less inhibition in the experimental groups than in the control (basal diet) group; and actinomycin D inhibited all groups similarly; while in the short-term experiments, puromycin induced less inhibition in the experimental groups than in the control group; actinomycin D inhibited the basal and ethionine groups more than the other groups; sparsomycin induced variable degrees of inhibition, with the ethionine group showing the most and the N-2-fluorenylacetamide and thioacetamide groups showing the least; hypertonic NaCl markedly inhibited all groups similarly; and CCl4 induced somewhat variable degrees of inhibition, with the thioacetamide group showing less than the other groups. In a few long-term experiments where hepatomas were evaluated in relation to surrounding liver tissue, puromycin administration induced less inhibition in the hepatomas than in the surrounding liver while actinomycin D administration induced similar inhibition in both groups. In general, in all experiments the degree of polyribosomal disaggregation was parallel to that of inhibition of protein synthesis (in vitro). The results reveal that the livers of rats fed purified diets containing selected hepatocarcinogens responsed in a variable manner in regard to protein synthesis (in vitro) and status of polyribosomal aggregation to the acute administration of selected hepatotoxic agents. (Author abstract) (23 Refs)

30. POLYCYCLIC AROMATIC HYDROCARBONS AND POSSIBLE METABOLITES: CONVERTOGENIC ACTIVITY IN YEAST AND TUMOR INITIATING ACTIVITY IN MOUSE SKIN.

Siebert D, Marquardt H, Friesel H, Hecker E

(c/o Hecker) Institut fur Biochemie, Deutsches Krebsforschungszentrum, D-6900 Heidelberg, W. Germany

J Cancer Res Clin Oncol; 102(2):127-139 1981

The diploid respiratory-deficient strain of yeast D4-RDII was used to assay PAH and urethane as well as some oxygenated derivatives of PAH and the (aliphatic) epoxide hydrolase inhibitor TCPO for convertogenic (mutagenic) activity. As a positive control, the convertogenic ultimate rat liver carcinogen NOAcAAF was used. PAH and urethane were found inactive as convertogens, TCPO was weakly active, whereas oxygenated electrophilic derivatives of PAH, such as K-region oxides, were found strong convertogens. For comparison, some convertogenic key compounds were assayed for their tumor-initiating activity in mouse skin in the standardized system using TPA as a promoter. PAH were stronger initiators than all oxygenated derivatives of PAH tested. TCPO alone exhibited very weak, if any, initiating activity. It was unable to modify initiation to any significant extent, if administered 5 min prior to administration of an initiator. In the absence of correlation between convertogenic and initiating activity the question of the chemical nature of 'ultimate initiators' of mouse skin carcinogenesis awaits further investigation. (Author abstract) (35 Refs)

31. EFFECTS OF PROLONGED ORAL TREATMENT WITH N-FLUOREN-4-YLACETOHYDROXAMIC ACID ON RAT LIVER FINE STRUCTURE.

Flaks B, Yost Y, Flaks A

Dept. Pathology, Univ. Bristol Medical Sch., Bristol BS8 1TD, England

Carcinogenesis; 3(1):103-109 1982

Inbred male Leeds strain rats were given a diet containing 0.05% N-fluoren-4-yla cetohydroxamic acid for up to 7 mo. A modified method for the synthesis of this compound is described. Rats were killed at intervals during and after treatment and their liver tissues examined by light and electron microscopy. The treated rats developed a very low incidence of (non-hepatic) tumors and hepatic clear cell foci appeared during the late stages of the experiment. The only significant fine structural changes observed were glycogenosis and alterations in the morphology of the rough endoplasmic reticulum, both of which developed only after prolonged treatment and affected a minority of hepatocytes. These changes are discussed in relation to the fine structural changes elicited by the strongly carcinogenic N-fluoren-2-ylacetamide and the non-carcinogen, N-fluoren-4-ylacetamide. (Author abstract) (29 Refs)

32. AMES TEST AND ANTITUMOR ACTIVITY OF 1-(X-PHENYL)-3,3-DIALKYLTRIAZENES: QUANTITATIVE STRUCTURE-ACTIVITY STUDIES BASED UPON MOLECULAR SHAPE ANALYSIS.

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Drug Design Group, Searle Res. and Development, G. D. Searle Co., Box 5110, Chicago, IL, 60680

Mol Pharmacol; 21(1):187-195 1982

Molecular shape analysis (MSA) was used as the basis of a quantitative structure-activity relationship (QSAR) study of two sets of 1-(X-phenyl)-3,3-dialkyltriazene compounds. Calculations were carried out with the CHEMLAB computing system, an expanded and more flexible version of CAMSEQ-II. The methodology and limitations of MSA and the steps in QSAR studies are reviewed; the technique is applied to 18 compounds (mutagenic in the Ames test) and 24 compounds (with reported antitumor potency) of the phenyltriazene group. Mechanisms of action are proposed based on QSAR results. Both mutagenic and antitumor activities seem to require the same 'active' shape of the phenyltriazenes, possibly to accommodate microsomal hydroxylation of the nitrogen methyl group. A therapeutic index (TI) was devised to maximize antitumor activity while minimizing mutagenicity, and a compound is predicted which maximizes TI. (13 Refs)

AMINO ACID ANALOGS AND MODIFIED NUCLEIC ACID CONSTITUENTS

33. REGULATION OF RAT ALPHA-FETOPROTEIN PRODUCTION BY METHIONINE DURING ETHIONINE-HEPATOCARCINOGENESIS.

Miyazaki M, Watanabe A

Div. Pathology, Cancer Inst., Okayama Univ., Okayama 700, Japan

Int J Cancer; 29(2):213-216 1982

The levels of serum alpha-fetoprotein (AFP) in rats were determined during hepatocarcinogenesis with ethionine, and the effects of methionine administration on serum AFP elevation in these animals were studied with the aim of investigating regulatory mechanisms of AFP production during carcinogenesis. Elevation of serum AFP was observed 6 wk following the start of feeding a diet containing 0.25% ethionine and again at the 22nd wk of feeding, when a well-differentiated hepatoma had already developed. These biphasic elevations of serum AFP concentrations in rats fed a 0.25% ethionine-containing diet decreased abruptly and significantly following a change to the basal diet either supplemented with or without 0.7% methionine. The possibility that regulation of AFP production in these rats may correlate with methionine metabolisms is discussed on the basis of the experimental data obtained. (Author abstract) (17 Refs)

34. INVESTIGATION OF THE TUMORIGENIC RESPONSE TO BENZO(A)PYRENE IN AQUEOUS CAFFEINE SOLUTION APPLIED ORALLY TO SPRAGUE-DAWLEY RATS.

Brune H, Deutsch-Wenzel RP, Habs M, Ivankovic S, Schmahl D
Biologisches Laboratorium, Vaselinwerk, Worthdamm 13-27, D-2000 Hamburg 11, W. Germany
J Cancer Res Clin Oncol; 102(2):153-157 1981

In a lifetime experiment benzo(a)pyrene (B(a)P) was administered to Sprague-Dawley rats either as an admixture to the diet or by gavage in an aqueous 1.5% caffeine soln. Dissolved benzo(a)pyrene induced more tumors of the forestomach than undissolved benzo(a)pyrene. The 1.5% caffeine soln (annual dose 27 g/kg) did not exert any carcinogenic activity under the conditions of this bioassay. (Author abstract) (17 Refs)

35. GENOTOXICITY OF COCOA EXAMINED BY MICROBIAL AND MAMMALIAN SYSTEMS.

Renner HW, Munzer R
Inst. Biochemistry, Federal Res. Centre for Nutrition, Engesserstr. 20, D-7500 Karl 5 ruhe, W. Germany
Mutat Res; 103(3-6):275-281 1982

The bone marrow sister-chromatid exchange (SCE) test, performed with implanted 5-bromodeoxyuridine tablets; the micronucleus test performed with outbred 10 to 14 wk-old Chinese hamsters; and the Ames test with Salmonella typhimurium (strains TA1535, TA100, TA1537, TA1538, TA98) were used to evaluate the genotoxicity of cocoa and two of its constituents: theobromine (ThB) and caffeine (CA). Not roasted cocoa administered by stomach tube at doses of 0.1-0.6 g/animal caused a dose-dependent elevation of bone-marrow SCEs; roasted cocoa (chocolate liquor) gave almost identical results. Extraction of the fat (47% of cocoa) almost doubled the number of SCEs at the highest cocoa dose, to 10.01/cell, and increased the number of SCEs at all other doses somewhat less (range 5.33-7.88 SCEs/cell). Cocoa butter and ThB- and fat-free cocoa caused no significant elevation of SCEs. ThB alone at doses of 2.5-20 mg/animal, and ThB + CA (6:1) at the same doses caused similar high levels of SCEs (4.77-9.50) in a dose-dependent way. The micronucleus test was negative for roasted and fat-free cocoa, 0.6 g/animal, but highly positive for ThB (doses 2 x 20, 30, or 40 mg ThB), but ThB (dose 1 x 20, 30, or 40 mg/animal) gave negative results in the chromosome aberration test. None of the Salmonella strains showed any mutagenic effect of cocoa at concentrations of 5.0, 2.5, 1.0, and 0.5%; greater than or equal to 5.0% cocoa was antibacterial. ThB at 0.25% gave no evid ence of mutagenicity with or without metabolic activation. ThB is evidently not demethylated in all mammals, and hence its non-mutagenicity cannot be assumed. (16 Refs)

36. THE TOXICOLOGY OF COCOA AND METHYLXANTHINES: A REVIEW OF THE LITERATURE.

Tarka SM
Life Sciences, Hershey Foods Corp., Corporate Technical Center, Hershey, PA
CRC Crit Rev Toxicol; 9(4):275-312 1982

Toxicology of cocoa and methylxanthines (caffeine, theobromine, and theophylline) was discussed with respect to the following: physical properties; toxic effects of cocoa and theobromine in the diets of various animals; biological effectiveness of the methylxanthines in cocoa; toxicity of methylxanthines; distribution, metabolism, and excretion in animals and humans (metabolism during pregnancy, lactation, and growth; diet and drug influence on methylxanthine metabolism); pharmacological properties of the methylxanthines; effects of methylxanthines on growth and other physiological processes; effects on reproduction; teratogenesis; mutagenesis; chronic toxicity/carcinogenesis; SCOGS report; and fibrocystic breast disease. Research on teratogenic and mutagenic effects of caffeine was thought to be relatively abundant, but there are only a few reports on the carcinogenic effects of caffeine and none on such effects of cocoa powder, theobromine, theophylline, or tea. (203 Refs)

37. MODIFICATION OF RADIATION-INDUCED DIVISION DELAY BY CAFFEINE ANALOGUES AND DIBUTYRYL CYCLIC AMP.

Kimler BF, Snyder MH, Rowley R, Schneiderman MH
Lab. Experimental Radiation Oncology, Thomas Jefferson Univ. Hosp., Philadelphia, PA, 19107
Int J Radiat Biol; 41(1):47-58 1982

The mitotic selection procedure for cell cycle analysis was utilized to investigate the concentration-dependent modification of radiation-induced division delay in Chinese hamster ovary (CHO) cells by methyl xanthines (caffeine, theophylline, and theobromine) and by dibutyryl cyclic AMP. The methyl xanthines (concentrations from 0.5 to 1,000 ug/ml) all reduced radiation-induced division delay with the effect being linear between approximately 100 and 1,000 ug/ml. After doses of 100-300 rad, delay was reduced by 75, 94 or 83% at 1,000 ug/ml for each drug, respectively. However, the addition of dibutyryl cyclic AMP had an opposite effect: radiation-induced delay was increased by the concentration range of 0.3 to 300 ug/ml. These results indicate that in mammalian cells the control of cell cycle progression and the modification of radiation-induced division delay are not simply related to intracellular levels of cyclic AMP. Rather, there appear to be at least two competing mechanisms which are differentially affected by caffeine analogues or by direct addition of dibutyryl cyclic AMP. The direct effect of caffeine and the methyl xanthines on membrane calcium permeability is considered. (Author abstract) (31 Refs)

38. MUTAGENICITY OF GAMMA-IRRADIATED OXYGENATED AND DEOXYGENATED SOLUTIONS OF 2-DEOXY-D-RIBOSE AND D-RIBOSE IN SALMONELLA TYPHIMURIUM.

Wilmer J, Schubert J, Leveling H
Div. Nutrition and Food Res., TNO, Dept. Biological Toxicology, P.O. Box 360, 3700 AJ Zeist, The Netherlands
Mutat Res; 90(4):385-397 1981

Mutagenic activity (MA) of soln of 2-deoxy-D-ribose (2DDR) and D-ribose (DR) irradiated under different conditions was studied in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538. Metabolic activation was provided by S9 mix prepared from liver homogenates from Wistar rats treated with Aroclor. Test soln were irradiated with gamma-radiation (0.12-0.14 kilogray(kGy)/min; total dose 10 kGy). Before and during irradiation highly purified O_2, N_2, or N_2O was bubbled through the soln. H_2O_2 present in irradiated oxygenated soln showed MA in TA98 and TA1537. MA of H_2O_2 was eliminated in the presence of S9. Irradiated soln of 2DDR or DR were mutagenic in TA98 and TA100 but not in the other strains. In the absence of S9, N_2O-saturated soln of 2DDR showed greater MA than N_2-saturated soln, suggesting that the OH radical is involved in production of mutagenic products of radiolysis. Malonaldehyde (MDA) was not mutagenic at concentrations produced by irradiation. MA of individual products of radiolysis were not determined. MA of irradiated 2DDR soln in TA100 increased with the level of aldehydes other than MDA. MA of irradiated 2DDR soln was reduced in a temperature-dependent manner by heating of the soln, supporting the hypothesis that MA is caused by carbonyl or dicarbonyl compounds. Autoclaved, nonirradiated soln of 2DDR showed no MA in S typhimurium. (22 Refs)

ALIPHATIC HALOGEN COMPOUNDS

39. RELATIONSHIP OF TISSUE NONPROTEIN SULFHYDRYLS TO THE ACUTE TOXIC EFFECTS OF 1,2-DIBROMO-3-CHLOROPROPANE.

Kluwe WM, Greenwell A, Harrington F
Natl. Toxicology Program, Natl. Inst. Environmental Health Sciences, P. O. Box 12233, Res. Triangle Park, NC, 27709
J Pharmacol Exp Ther; 220(2):399-405 1982

Acute sc treatment of Fischer rats with 1,2-dibromo-3-chloropropane (DBCP) caused a dose-dependent depletion of hepatic but not renal or testicular nonprotein sulfhydryls (NPS). The liver is apparently the major site of formation of glutathione conjugates excreted in the urine as mercapturic acids. Because the sites of DBCP tissue injury, principally kidney and testis, do not coincide with the site of NPS depletion, local glutathione depletion does not seem to be a prerequisite for tissue injury. A significant loss of hepatic glutathione may be the critical element in determining the threshold for acute DBCP-induced renal and testicular injury. (32 Refs)

40. CONTAMINATION OF DRINKING WATER BY ORGANIC CHEMICALS.

Gaston JM
No affiliation given
West J Med; 136(1):45-46 1982

The use of dibromodichloropropane (DBCP), an agricultural nematocide, was prohibited in California in 1977. However, significant contamination of groundwater and drinking water by DBCP (0.5-60 ppm) has been discovered. Trichloroethylene (TCE), a widely used industrial degreasing agent, while thought to be less active and much less dangerous than DBCP, has been found in higher levels in groundwater (1-1,000 ppb). TCE is now regarded as a potential human carcinogen. Because a zero concentration in drinking water may be impracticable or impossible to achieve, appropriate cancer risk levels should be calculated. (3 Refs)

41. EVIDENCE FOR CARBON TETRACHLORIDE-INDUCED LIPID PEROXIDATION IN MOUSE LIVER.

Lee PY, McCay PB, Hornbrook KR
Dept. Pharmacology, Univ. Oklahoma Health Sciences Center, P.O. Box 26901, Oklahoma City, OK, 73190
Biochem Pharmacol; 31(3):405-409 1982

The involvement of lipid peroxidation in the mechanism of carbon tetrachloride-induced hepatotoxicity has been a point of controversy. Previous investigators have reported an absence of lipid peroxidative degradation products in mice after exposure to carbon tetrachloride and have used this evidence against the hypothesis that lipid peroxidation is an integral part of the events that cause tissue damage. We have compared the extent of lipid peroxidation caused by carbon tetrachloride between Sprague-Dawley rats and three strains of mice (A/J, BALB/cJ, and C57Bl/6J) in in vitro and in vivo systems. Hepatic microsomes isolated from fasted mice of each strain produced more malondialdehyde (a degradation product of lipid peroxidation) per mg microsomal protein than those isolated from fasted rats at all times of incubation with CCl4. In vivo lipid peroxidation was estimated by the lipid conjugated diene content in hepatic microsomes from the rat and three strains of mice. Increased conjugated diene formation was observed in microsomal lipids of these animals after intraperitoneal injection of CCl4 (1 ml/kg as a 20% solution in corn oil) when compared to animals given only corn oil, but no differences were found in the amount of conjugated dienes between mice and rats. Our observations show that the CCl4-treated mouse undergoes hepatic lipid peroxidation at least as well as the rat, and indicate that lipid peroxidation cannot be excluded as a mechanism of carbon tetrachloride hepatotoxicity as has been claimed on the basis of its ineffectiveness in the mouse. (Author abstract) (25 Refs)

42. 1,1-DICHLOROETHYLENE-INDUCED PULMONARY INJURY.

Forkert PG, Reynolds ES
Dept. Pathology, Univ. Texas Medical Branch, Galveston, TX, 77550
Exp Lung Res; 3(1):57-68 1982

Administration of 1,1-dichloroethylene (100 or 200 mg/kg via gastric tube) to male C57B1/6 mice caused severe pulmonary injury. Necrosis of ciliated and Clara cells and exfoliation of bronchiolar lining were observed 6 hr after administration of 200 mg/kg; pulmonary edema, hemorrhage, and focal atelectasis were present at 24 hr. Significant hypoxia was associated with the pulmonary injury. By 7 days posttreatment, epithelial lining had recovered. (41 Refs)

43. REACTIVE METABOLITES AND CARCINOGENICITY OF HALOGENATED ETHYLENES.

Bolt HM, Laib RJ, Filser JG
Pharmakologisches Institut, Abteilung Toxikologie, Johannes Gutenberg-Universitat Mainz, Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany
Biochem Pharmacol; 31(1):1-4 1982

Mutagenicity and carcinogenicity of halogenated ethylenes (HE) are reviewed with special emphasis on the role of molecular rearrangement in metabolic detoxication. Comparison of the data on the formation of hepatic preneoplastic foci after exposure of young Wistar rats to HE with the metabolic data showed significant reduction of the wide range of oncogenic activities when the preneoplastic effects were related to the amount of HE metabolites produced after 400 hr of exposure. It is suggested that monochlorooxirane (the epoxide of vinyl chloride) represents an optimum between stability and reactivity to reach the DNA target and react with it. (47 Refs)

44. ETHYLENE DIBROMIDE (EDB). (REVISED).

NIOSH Document Development Branch
Robert A. Taft Lab., National Inst. Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH, 45226
Curr Intell Bull NIOSH (37): 13 pp., 1981.

Toxic and carcinogenic effects of ethylene dibromide (EDB) are reviewed. Recent experimental data has reinforced the conclusion that EDB is carcinogenic in animals and that EDB should be treated as a potential occupational carcinogen in the workplace. A ceiling limit of 0.13 ppm (1.0 mg/cubic meter) over any 15 min sampling period and use of appropriate controls to reduce worker exposure are recommended. Studies have shown a high mortality rate and a statistically significant increase in incidence of benign and malignant tumors of the spleen, mammary gland, and nasal cavity in rats exposed to EDB by inhalation at 20 ppm and fed the standard rat diet. Addition of disulfiram (0.05% by wt) to the diet resulted in an approx ten-fold increase in incidence of hepatocellular carcinomas over exposure to EDB alone. The increased interaction may not necessarily be restricted to disulfiram but may occur with similarly structured compounds such as Thiram, a fungicide and seed disinfectant. Epidemiologic studies of EDB in humans have been inconclusive because of small cohort size, incomplete or missing exposure data, and insufficient latencies to observe carcinogenic effects. Gaseous EDB at concentrations ranging from 0.2 to 2 ppm induced significant numbers of sex-linked recessive lethal mutations in Drosophila melanogaster males. Mutation induction was directly proportional to both exposure time and exposure concentration up to 60 ppm-hr for all cell stages tested. (16 Refs)

45. CHLORINATED PARAFFINS; RESPONSE TO THE INTERAGENCY TESTING COMMITTEE.

Hernandez JW
(c/o John B. Ritch), Environmental Protection Agency, 401 M St. S.W., Washington, DC, 20460
Fed Regist; 47(5):1017-1019 1982

In the initial report of the Interagency Testing Committee (ITC), transmitted to the EPA on October 4, 1977, the Committee recommended to the Administrator of the EPA the chemical category 'chlorinated paraffins' for consideration for testing. Earlier that year, an international group of chlorinated paraffin manufacturers had formed a Consortium to test their products for both health and environmental effects. The EPA has discussed the planned testing with the Consortium and finds the proposal from the Consortium to test chlorinated paraffins voluntarily for their health and environmental effects to be acceptable. Consequently, the EPA is not at this time proposing a section 4(a) rule to require health or environmental effects testing of the chlorinated paraffins. (Author abstract) (no Refs)

POLYHALOGENATED RING COMPOUNDS INCLUDING INSECTICIDES

46. METHODS FOR THE RECOVERY OF ORGANIC CARCINOGENS FROM WATER.

Ehrlich K, Cawley G, Klein E
Gulf South Res. Inst., New Orleans, LA
Methods for the Recovery of Organic Carcinogens from Water. Available from National Technical Information Service, Springfield, VA, as PB81-209694:, 41 pp., 1981.

The organic carcinogens benzo(a)pyrene, dieldrin, and N-acetyl-2-aminofluorene were recovered on XAD-2 macroreticular resin in yields of 90% or more from distilled water or seawater and in yields of 40% or more from Lake Pontchartrain water containing a high concentration of organic material. The original solutions contained less than 500 parts per trillion of carcinogen. These results show that XAD-2 provides an efficient means for recovering nonpolar organic carcinogens from dilute solutions. More polar carcinogens such as dimethylnitrosamine were not effectively recovered on XAD-2 columns. Since XAD-2 binding would not be selective for carcinogens, the authors investigated methods which might bind carcinogens selectively from a mixture of organic compounds. We tested the ability of the above carcinogens to bind to nucleic acid using direct binding, equilibrium dialysis, nuclei binding, and binding to DNA-cellulose. Radio-labeled carcinogens were used to quantify the amount bound. Either rat liver nuclei (0.1 mg DNA) or DNA-cellulose (1 mg DNA) bound 18% of the acetylaminofluorene and up to 66% of the dieldrin from solutions containing 150 to 280 nmoles of compound. Up to 30% of the benzo(a)pyrene from solutions containing as much as 320 pmoles was bound. Tenfold or lower recoveries were found when direct-binding methods were used. (Author abstract)

47. EFFECTS OF DICHLORODIPHENYLTRICHLOROETHANE AND ITS ANALOGUES ON RAT LIVER MITOCHONDRIA.

Ohyama T, Takahashi T, Ogawa H
Hokkaido Inst. Public Health, N. 19, W. 12, Kita-Ku Sapporo 060, Hokkaido, Japan
Biochem Pharmacol; 31(3):397-404 1982

The effects of dichlorodiphenyltrichloroethane (DDT) and 16 analogues on respiration, swelling and latent ATPase of rat liver mitochondria were examined systematically. The compounds tested could be divided into four groups: DDT-type, DDE-type, kelthane-type and others by substituent groups on the ethane bridge of bis(p-chlorophenyl) ethane. Most compounds tested were shown to inhibit State 3 respiration. A linear relation was observed between the logarithms of the concentrations giving half-inhibition of State 3 respiration and the logarithms of the partition coefficients of the tested compounds. Four compounds of the kelthane type and chlorobenzilate stimulated State 4 respiration to the level of dinitrophenol-stimulated respiration. The compounds that have a hydroxy group on the ethane bridge rapidly induced mitochondrial swelling, but DDT-type and DDE-type compounds induced swelling when the suspension contained 0.15 M KCl and 5 mM Tris-HCl. Latent ATPase of mitochondria was stimulated to different max levels by each of the tested compounds except DDA. The oligomycin-sensitive ATPase of submitochondria was inhibited by a series of kelthane-type compounds. (Author abstract) (41 Refs)

48. PROMOTION BY POLYCHLORINATED BIPHENYLS OF ENZYME-ALTERED FOCI IN RAT LIVER.

Pereira MA, Herren SL, Britt AL, Khoury MM
Health Effects Res. Lab., U.S. Environmental Protection Agency, 26 West St. Clair St., Cincinnati, OH, 45267
Cancer Lett; 15(2):185-190 1982

The number of gamma-glutamyltranspeptidase (GGTase)-positive foci was examined in livers of partially hepatectomized male Sprague-Dawley rats given an initiating dose of diethylnitrosamine (DENA: 0.3 millimole/kg body wt, po) followed 7, 28, or 49 days later by one to three doses of Aroclor 1254 (500 mg/kg, ip). Rats were killed 21 days after the last dose of Aroclor. Incidence of GGTase-positive foci increased from a mean of 0.70 foci/square cm (cm2) liver in solvent (tricaprylin)-treated, partially-hepatectomized, DENA-initiated controls to 2.28 foci/cm2 in animals given a single dose of Aroclor 1254. Maximum enhancement was obtained after two doses, which resulted in 3.47 foci/cm2. Up to three doses of Aroclor did not increase the incidence of GGTase-positive foci in partially-hepatectomized animals that had not received DENA. Aroclor 1254 appears suitable as an inexpensive promotor in a short-term initiation/promotion assay for chemical carcinogens. (20 Refs)

49. MUTAGENIC EFFECTS OF COMBINATIONS OF CHEMICAL CARCINOGENS AND ENVIRONMENTAL POLLUTANTS IN MICE AS SHOWN BY THE MICRONUCLEUS TEST.

Watanabe M, Honda S, Hayashi M, Matsuda T
Dept. Community Medicine, Toyama Medical and Pharmaceutical Univ., Toyama, Japan
Mutat Res; 97(1):43-48 1982

Combinations of dimethylnitrosoamine (DMN) or N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and CdCl2 or polychlorinated biphenyls (PCB) were force-fed to male ddY mice. The Schmidt method of determining polychromatic erythrocytes (PCEs) in bone marrow cells was used to measure mutagenicity. DMN alone gave a clear dose-dependent response, whereas Cd alone did not; Cd + DMN enhanced the PCE frequency over that for the equivalent concentration of DMN alone. Possible enhancement of MNNG effects by Cd was also observed. PCB alone had almost no effect, and no synergistic or additive effect with DMN or MNNG was seen. Corn oil seemed to inhibit DMN activity. The results suggest that some combinations of carcinogens and environmental pollutants can interact in mutagenic activity. (4 Refs)

BENZENE DERIVATIVES

50. POTENTIAL IDENTIFICATION OF CHEMICAL CARCINOGENS IN A VIRAL TRANSFORMATION SYSTEM.

Wilson WW, Khoobyarian N
(c/o Khoobyarian) Dept. Microbiology and Immunology, Sch. Basic Medical Sciences, Univ. Illinois at Medical Center, P.O. Box 6998, Chicago, IL, 60680
Chem Biol Interact; 38(2):253-259 1982

Chemical carcinogens from several diverse chemical classes ie; aromatic amines, polycyclic hydrocarbons, nitrosamines, hormonal derivatives, metals and direct alkylating agents cause a 6.2-60.5-fold increase in the frequency of murine sarcoma virus (MSV)-induced transformation in a normal rat kidney (NRK) cell system. Exogenous metabolic activation with a rat liver S-9 homogenate is required for expression of this activity by procarcinogens. Non-carcinogenic analogs of these compounds fail to cause significant increases in the transformation frequency either with or without prior metabolic activation. Iododeoxyuridine, a mutagen also does not cause enhancement of transformation. This system may serve as the basis for a rapid and quantifiable means of identifying chemical carcinogens while introducing a new model for the understanding of the interactions between oncornaviruses and chemical carcinogens. (Author abstract) (14 Refs)

51. MUTAGENICITY OF STYRENE IN THE SALMONELLA TYPHIMURIUM TEST SYSTEM.

de Meester C, Duverger-van Bogaert M, Lambotte-Vandepaer M, Mercier M, Poncelet F
Unite TBCM, Sch. Pharmacy, Univ. Louvain, UCL/72.37, 72, Ave. E. Mounier, B-1200 Brussels, Belgium
Mutat Res; 90(4):443-450 1981

Seven strains of Salmonella typhimurium were exposed to gaseous styrene. Styrene produced mutagenic effects in strains TA1530, TA1535, and TA100; mutagenesis required the presence of S^9 fr om rats treated with Aroclor. A dose-effect relationship was established in TA1530. Mutagenic activity of styrene was weak. Results indicate formation of a volatile, unidentified intermediate compound by S9 enzymes. (22 Refs)

52. TOXICOLOGY, INDUSTRIAL HYGIENE AND MEDICAL CONTROL OF TD1, MD1 AND PMPPI.

Woolrich PF
Upjohn Co., 7171 Portage Road, Kalamazoo, MI, 49001
Am Ind Hyg Assoc J; 43(2):89-97 1982

A comprehensive review of physiologic effects, toxicology, industrial hygiene, and medical control of isocyanates used to manufacture polyurethanes and polyisocyanurates is presented. The most significant effect of exposure to toluene diisocyanate (TDI), methyl bisphenylisocyanate (MDI), or polymethylene polyphenylisocyanate is a direct irritant or sensitization response. Experiments in which TDI and MDI were tested for mutagenicity and carcinogenicity are summarized. Neither chemical consistently produced positive results in the Ames test. No evidence of carcinogenicity was obtained for either compound. (33 Refs)

53. BIOCHEMICAL TOXICOLOGY OF BENZENE.

Snyder R, Longacre SL, Witmer CM, Kocsis JJ, Andrews LS, Lee EW
Dept. Pharmacology, Thomas Jefferson Univ., Philadelphia, PA, 19107
Rev Biochem Toxicol; 3:123-153 1981

In vitro and in vivo metabolism of benzene (BZ) and new studies on the hemopoietic toxicity of BZ are reviewed. Information relating the metabolism of BZ to its toxicity is used to postulate a mechanism whereby BZ produces blood dyscrasias. Exposure to BZ produces a number of changes in the peripheral blood and bone marrow that may eventually result in the development of aplastic anemia. Recent epidemiological studies have confirmed earlier reports that workers exposed to BZ are at increased risk of developing cancer of the hemopoietic system. Recent studies indicate that BZ metabolites mediate the hemopoietic toxicity of BZ. (125 Refs)

54. THE UKEMS GENOTOXICITY TRIAL. A SUMMARY OF THE ASSAYS FOR SKIN TUMOUR INDUCTION IN MICE, THE SUBCUTANEOUS IMPLANT TEST AND THE SEBACEOUS GLAND SUPPRESSION TEST.

Coombs MM
Imperial Cancer Res. Fund Lab., P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England
Mutat Res; 100(1-4):407-409 1982

Studies of skin tumor induction by 4-chloromethylbiphenyl, 4-hydroxymethylbiphenyl, and benzyl chloride are reviewed. Mice were treated by repeated topical application of test compounds, single application followed by application of tumor promoters, or sc implantation of test chemicals. Results indicate that none of the test compounds are strongly carcinogenic; further time is required to confirm possible weak carcinogenicity. (8 Refs)

55. THE UKEMS COLLABORATIVE GENOTOXICITY TRIAL ORGANISATION, SELECTION CRITERIA AND PREPARATION OF THE CHEMICALS.

Ashby J, Parry JM, Arlett CF, Coombs MM
Central Toxocology Lab., ICI Ltd., Alderley Edge, Macclesfield, Cheshire, England
Mutat Res; 100(1-4):1-6 1982

The United Kingdom Environmental Mutagen Society (UKEMS) set up four bioassays, three carcinogenicity tests, and a dominant lethal assay, each in mice to determine the mutagenicity of benzyl chloride, 4-chloromethylbiphenyl, and 4-hydroxymethylbiphenyl. Characteristics, analyses, and sources of test chemicals are reported. Operation of the trial is described. (6 Refs)

56. AN OVERVIEW OF THE CHEMICAL AND BIOLOGICAL REACTIVITY OF 4CMB AND STRUCTURALLY RELATED COMPOUNDS: POSSIBLE RELEVANCE TO THE OVERALL FINDINGS OF THE UKEMS 1981 STUDY.

Ashby J, Lefevre PA, Elliott BM, Styles JA
Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Park, Macclesfield, Cheshire, England
Mutat Res; 100(1-4):417-433 1982

Negative mutagenicity results for 4-chloromethylbiphenyl (4CMB) obtained during collaborative studies are discussed. Topics include bacterial mutagenicity of 4CMB with respect to structurally-related analogs of biphenyl, metabolic detoxification of 4CMB, the effect of 4CMB on thermal denaturation of calf thymus DNA, hydrolysis of 4CMB to 4-hydroxymethylbiphenyl (4HMB), activity of 4CMB relative to benzyl chloride (BC), detoxification of 4CMB by 'non-critical' macromolecules, and derivatives of 4CMB with altered chemical stability. Addition of a benzene ring to BC to yield 4CMB is apparently accompanied by a marked increase in genotoxic activity in vitro and a decrease in hydrolytic stability, such that 4CMB may be quickly transformed into 4HMB. Awareness of the hydrolytic stability of a new alkylating agent and knowledge of its aqueous/lipid partition coefficient, its stability in S9, and responses observed in a variety of modifications of the Salmonella assay are required for estimation of genotoxic potency in vivo. (19 Refs)

57. THE GENETIC TOXICOLOGY OF 4-CHLOROMETHYLBIPHENYL (4CMB), 4-HYDROXYMETHYLBIPHENYL (4HMB), AND BENZYL CHLORIDE (BC) AS ASSESSED BY THE UKEMS GENOTOXICITY TRIAL (1981).

Parry JM
Dept. Genetics, Univ. Coll. Swansea, Swansea SA2 8PP, Wales
Mutat Res; 100(1-4):411-416 1982

Studies of the genetic toxicology of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethybiphenyl (4HMB), and benzyl choride (BC) are reviewed. Bacterial studies showed that 4CMB is a strong, direct-acting mutagen. 4CMB produces frame-shift and base-pair mutations, apparently by different mechanisms. In fungi 4CMB produced point mutations, mitotic gene conversions, primary DNA damage, and mitotic crossing-over; the presence of metabolic activation systems (MAS) reduced overall toxicity without affecting genetic effects of 4CMB. In mammalian cell cultures 4CMB produced repairable DNA damage, point mutations, chromosome aberrations, and sister chromatid exchanges. In vivo studies did not show that 4CMB induces dominant lethal mutations, micronuclei, aberrations of sperm morphology, or skin tumors. Initial findings suggest that 4CMB may be a weak skin carcinogen. Bacterial studies showed BC to be mutagenic with approx 10% of the base-pair substitution activity of 4CMB. The mutagenic activity of BC increased in the presence of MAS. In fungi BC had mutagenic activity similar to 4CMB. In mammalian cell cultures BC had approx 20% of the activity of 4CMB. No evidence of skin carcinogenicity has been found after 10 mo. No evidence for mutagenicity of 4HMB was found in any system tested. Overall results indicate the value of a range of tests in determining genetic toxicology of compounds. (8 Refs)

58. UKEMS COLLABORATIVE GENOTOXICITY TRIAL: CYTOGENETIC TESTS OF 4CMB, BC AND 4HMB: SUMMARY AND APPRAISAL.

Scott D
Paterson Lab., Christie Hosp., Manchester M20 9BX, England
Mutat Res; 100(1-4):313-331 1982

Studies of the genotoxic potential of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) in vitro and of 4CMB in vivo are reviewed. Trials used eight different systems (cultured rat-liver epithelial cells, Chinese hamster V79 and bone marrow cells, human lymphocytes and fibroblasts, and mouse bone marrow cells in vitro, and mouse spermatocytes and oocytes in vivo). Aberrations in chromosomal structure (CA) and sister chromatid exchanges (SCE) were produced by 4CMB and BC but not 4HMB. No consistent differences in effectiveness were found between 4CMB and BC. Changes in chromosome number were not produced by any of the test compounds. 4CMB produced greater increases in CA and SCE in the presence of metabolic activation systems (in rat liver epithelial cells or in the presence of S9 mix) than in the absence of such systems. Since 4CMB does not require activation, the findings suggest that under certain conditions 4CMB can be converted to a more potent electrophile. Overall results indicate that 4CMB is a weak mutagen. (16 Refs)

59. UKEMS GENOTOXICITY TRIAL 1981. IN VIVO ASSAY SYSTEMS.

Topham JC
Pharmaceuticals Div., Safety Medicines Dept., Imperial Chemical Industries Ltd., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, England
Mutat Res; 100(1-4):381-387 1982

In vivo studies of the mutagenicity of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) are reviewed. 4CMB was tested in 14 systems, 4HMB in 8 systems, and BC in 9 systems. All three compounds were tested by the micronucleus test (with administration po, ip, and sc), F1 sperm-head morphology test (with administration sc and ip), sex-linked recessive lethal test (SLRL), and somatic cell misregulation test (both by po administration). Only 4CMB was tested by the dominant lethal test and the transplacental micronucleus test in mice. Assays in mice did not yield positive results for any of the test compounds. All three compounds produced dose-related toxic effects in mice. 4CMB was more toxic in females than in males. SLRL in Drosophila melanogaster in different laboratories produced contradictory results: some marginally positive results for all three compounds could not be reproduced. Overall results indicate no mutagenicity in mice. No firm evidence of mutagenicity with SLRL was found. All three compounds showed positive results in somatic cell misregulation tests in D melanogaster. (1 Ref)

60. ASSESSMENT OF THE ABILITY OF 4CMB AND 4HMB TO INDUCE PRIMARY GENETIC DAMAGE IN STRAINS OF ESCHERICHIA COLI.

May K, Lodge DC, Bootman J
Life Science Res., Stock, Essex CM4 9PE, England
Mutat Res; 100(1-4):9-13 1982

The ability of 4-chloromethylbiphenyl (4CMB) and 4-hydroxymethylbiphenyl (4HMB) to induce primary DNA damage in bacteria as shown by differential lethality in strains of Escherichia coli proficient and deficient in DNA repair was examined. E coli strain WP2 and its derivatives WP67 (uvrA-, polA-) and CM871 (uvrA-, recA-, lexA-) were used to assess comparative survival. Selective toxicity of both 4CMB and 4HMB towards the trebly repair-deficient strain CM871 was evident after 2 and 18 hr. Some evidence of toxicity of 4CMB towards WP67 was obtained after 2 hr, but this was more evident after 18 hr of exposure. Similar results were obtained in the presence and absence of S9 mix. Results obtained with the positive controls, 2-aminoanthracene and mitomycin C confirmed the characteristics of the bacterial strains and the activity of the S9 mix. 2-Aminoanthracene was selectively toxic to the CM871 but only in the presence of S9 mix. Direct action of both 4CMB and 4HMB was demonstrated. 4CMB was more lethal to CM871 than to WP67 while 4HMB was equitoxic to both repair-deficient strains; this may indicate that both chemicals produce DNA damage recognized by the uvrA system and that 4CMB also produces damage recognized or repaired by the recA or lexA systems. (1 Ref)

61. MUTAGENICITY OF 4-CHLOROMETHYLBIPEHNYL (4CMB) TO E. COLI WP2 UVRA PKM101.

Penman MG
Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Park, Nr. Macclesfield, Cheshire, England
Mutat Res; 100(1-4):15-16 1982

An Escherichia coli (strain WP2 uvrA pKM101) plate-incorporation assay was used to test the mutagenicity of the potential carcinogen 4-chloromethylbiphenyl (4CMB). A positive response was observed in the absence of S9, with a max response at 500 ug/plate. (1 Ref)

62. MUTAGENIC ACTIVITY OF BC AND 4CMB IN THE SALMONELLA SPOT TEST.

Hyldig-Nielsen F, Hartley-Asp B
Microbiology Dept., H. Lundbeck and Co., Valby, DK-2500 Copenhagen, Denmark
Mutat Res; 100(1-4):17-19 1982

The Salmonella spot test was used to test the mutagenicity of benzylchloride (BC) and 4-chloromethylbiphenyl (4CMB). 4CMB exhibited mutagenic activity in TA1538, TA98, and TA100 whereas BC was only active in TA100. 4CMB was active in TA100 at a lower concentration than BC. Thus, 4CMB exhibited a higher mutagenic potential than BC in the Salmonella typhimurium spot test. (1 Ref)

63. BACTERIAL MUTAGENICITY TESTS ON 4-CHLOROMETHYLBIPHENYL AND 2 STRUCTURAL ANALOGUES.

Kirkland DJ, Smith KL, Parmar V
Toxicol Lab. Ltd., Bromyard Road, Ledbury, Herefordshire, HR8 ILG, England
Mutat Res; 100(1-4):21-25 1982

Mutagenic activity of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzylchloride (BC) was assayed in five strains of Salmonella typhimurium and two strains of Escherichia coli using the Ames plate-incorporation method for reversion to His+ in Salmonella, and a modified method for reversion to Trp+ in E coli. 4CMB showed strong mutagenicity causing both frameshift and base-pair substitution mutations. BC was a weak base substitution mutagen. 4HMB showed neither base substitution nor frameshift mutagenic activity. (4 Refs)

64. 4-CHLOROMETHYLBIPHENYL (4CMB), BENZYL CHLORIDE (BC) AND 4-HYDROXYMETHYLBIPHENYL (4HMB): REVERSE MUTATION TESTS WITH SALMONELLA TYPHIMURIUM.

Ladner A
Toxicology Dept., Fisons Ltd., Loughborough, Leicestershire, England
Mutat Res; 100(1-4):27-31 1982

In vitro mutagenic activities of benzyl chloride (BC), 4-chloromethylbiphenyl (4CMB), and 4-hydroxymethylbiphenyl (4-HMB) were compared. 4CMB produced strong mutagenic responses in Salmonella typhimurium strains TA1538 and TA98. Positive but somewhat weaker responses were also obtained with the third frame-shift detector TA1537. Tests with the two base-pair substitution detector strains gave conflicting results. 4CMB was strongly mutagenic for strain TA100 while results with TA1535 were equivocal. Slight indications of positivity were obtained with strain TA100 for BC. No evidence of genetic activity was seen in any of the five tester strains for 4HMB. (6 Refs)

65. ACTIVITY OF 4CMB AND 4HMB IN BACTERIAL MUTATION ASSAYS.

Lodge DC, Bootman J, May K
Life Science Res., Stock, Essex CM4 9PE, England
Mutat Res; 100(1-4):33-34 1982

Mutagenicities of 4-chloromethylbiphenyl (4CMB) and 4-hydroxymethylbiphenyl (4HMB) were determined in conventional pour-plate tests for chemical levels of 1.6-1,000 ug/plate. 4CMB was directly active in all tests, inducing both frameshift and base substitution mutations. Inclusion of S9 mix did not significantly affect 4CMB-induced responses. 4HMB was inactive in all experiments. (1 Ref)

66. EVALUATION OF 4-HYDROXYMETHYLBIPHENYL (4HMB), 4-CHLOROMETHYLBIPHENYL (4CMB) AND BENZYL CHLORIDE (BC) USING THE AMES SALMONELLA/MICROSOME INCORPORATION TEST FOR MUTAGENICITY.

Moore WB, Chatfield SN
Dept. Bacteriology, Wellcome Res. Lab., Langley Court, Beckenham, Kent BR3 3BS, England
Mutat Res; 100(1-4):35-38 1982

Abilities of 4-chloromethylbiphenyl (4CMB), benzyl chloride (BC), and 4-hydroxymethylbiphenyl (4HMB) to effect point mutations at histidine loci in each of five specially constructed strains of Salmonella typhimurium (TA1535, TA1537, TA1538, TA98, and TA100) were determined in vitro using the Ames Salmonella/microsome incorporation test. The results indicated that 4HMB is neither a direct nor pro-mutagen, 4CMB is a direct mutagen, and BC is a direct mutagen of low potency. (3 Refs)

67. UKEMS TRIAL: BACTERIAL MUTATION TESTS OF 4-CHLOROMETHYLBIPHENYL, 4-HYDROXYMETHYLBIPHENYL, AND BENZYL CHLORIDE, USING E. COLI WP2UVRA(PKM101) AND S. TYPHIMURIUM TA98 AND TA100.

Venitt S, Crofton-Sleigh C, Bosworth DA
Pollards Wood Res. Station, Chester Beatty Res. Inst., Inst. Cancer Res., Nightingales Lane, Chalfont St. Giles, Bucks HP8 4SP, England
Mutat Res; 100(1-4):39-43 1982

Mutagenicity plate tests using Escherichia coli WP2uvrA(pKM101) and Salmonella typhimurium TA98 and TA100 were performed on 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC). 4CMB was tested in WP2uvrA(pKM101) using the microtiter fluctuation test. In the plate tests, 4CMB was reproducibly mutagenic to all three strains, BC was reproducibly mutagenic to TA100 and WP2uvrA(pKM101), and 4HMB was uniformly negative in all three strains. Fluctuation tests indicated that 4CMB ages in dimethylsulfoxide solutions even when kept frozen. (4 Refs)

68. UKEMS TRIAL COMPOUNDS: IN VITRO BACTERIAL MUTAGENICITY.

Varley RB
Res. Dept., Boots Co. Ltd., Pennyfoot St., Nottingham, NG2 3AA, England
Mutat Res; 100(1-4):45-47 1982

Mutagenicities of 4-chloromethylbiphenyl (4CMB), benzyl chloride (BC), and 4-hydroxymethylbiphenyl (4HMB) were determined in the Ames test using Salmonella typhimurium TA1535, TA1537, TA98 and TA100. 4CMB elicited dose-related mutagenic activity against all of the listed tester strains in the presence of S9 mix, but was active against only TA1538, TA98, and TA100 in the absence of the activation system. In one assay with TA100, BC produced isolated increases in the numbers of revertant colonies in the presence of S9. 4HMB showed no evidence of mutagenicity. (4 Refs)

69. 4-CHLOROMETHYLBIPHENYL (4CMB), BENZYL CHLORIDE (BC) AND 4-HYDROXYMETHYLBIPHENYL (4HMB): AN EVALUATION OF THEIR MUTAGENIC POTENTIAL USING SALMONELLA TYPHIMURIUM.

Jones E, Richold M
Dept. Mutagenesis, Huntingdon Res. Centre, Huntingdon, Cambridgeshire, PE18 6ES, England
Mutat Res; 100(1-4):49-54 1982

Of three compounds tested using the Ames Salmonella typhimurium mutagenicity assay, only 4-chloromethylbiphenyl (4CMB) produced a strong positive response. No substantial increases in revertant colonies were observed following treatment with either benzyl chloride (BC) or 4-hydroxymethylbiphenyl (4HMB). No substantial increases in revertant colonies were observed following treatment with urine from mice dosed with 4CMB, BC, or 4HMB. The results indicated that the mutagenicity of 4CMB is considerably reduced, if not removed, when in vivo mutagenicity tests are used. (5 Refs)

70. 4-CHLOROMETHYLBIPHENYL, 4-HYDROXYMETHYLBIPHENYL AND BENZYL CHLORIDE: A COMPARISON OF MUTAGENIC POTENTIAL USING THE SALMONELLA REVERSE MUTATION ASSAY.

Trueman RW, Callander RD
Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Park, Macclesfield, Cheshire, England
Mutat Res; 100(1-4):55-59 1982

The Salmonella reverse mutation assay was used to determine the mutagenicity of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC). 4CMB gave a positive response in all five Salmonella tester strains, both in the presence and absence of S9. 4HMB gave a negative response in the presence of S9 with all strains. BC failed to give a positive response in any of the five strains in the absence of S9 mix. (2 Refs)

71. THE MUTAGENIC ACTIVITY OF 4-CHLOROMETHYLBIPHENYL (4CMB) AND BENZYL CHLORIDE (BC) IN THE BACTERIAL/MICROSOME ASSAY.

Brooks TM, Gonzalez LP
Sittingbourne Res. Centre, Shell Res. Ltd., Sittingbourne, Kent, ME9 8AG, England
Mutat Res; 100(1-4):61-64 1982

The mutagenic activity of 4-chloromethylbiphenyl (4CMB) was studied in agar layer cultures of Salmonella typhimurium TA1535, TA1537, TA1538, TA98, and TA100, and Escherichia coli WP2 and WP2uvrA. The mutagenic activity of benzyl chloride (BC) was investigated in only Salmonella strains. Assays were performed with or without S9 activation. The results indicated that 4CMB is a direct-acting bacterial mutagen that shows a greater response in strains TA1538 and TA98, and that this activity is reduced in the presence of the S9 fraction. BC is a bacterial mutagen in strain TA100 only and the mutagenic response is increased by S9 mix. (4 Refs)

72. MUTAGENIC STUDIES ON BENZYL CHLORIDE, 4-CHLOROMETHYLBIPHENYL AND 4-HYDROXYMETHYLBIPHENYL WITH SALMONELLA TYPHIMURIUM AS PART OF THE UKEMS TRIAL.

Watkins P, Rickard C
Pharmaceuticals Div., Imperial Chemical Industries Ltd., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, England
Mutat Res; 100(1-4):65-66 1982

Mutagenicities of benzyl chloride (BC), 4-chloromethylbiphenyl (4CMB), and 4-hydroxymethylbiphenyl (4HMB) were determined in histidine-dependent strains (TA1535, TA1537, TA1538, TA98, and TA100) of Salmonella typhimurium using a plate incorporation assay and S9 mix. BC showed a positive mutagenic response only with TA100 and only in the presence of S9 mix. 4CMB gave positive results with strains TA100, TA1535, and TA1538, with or without S9 mix. With strains TA98 and TA1537, 4CMB only gave a positive response in the presence of S9 mix. 4HMB showed no positive results with any of the strains tested. (1 Ref)

73. MUTAGENICITY OF 4-CHLOROMETHYLBIPHENYL IN THE SALMONELLA/MICROSOME ASSAY.

Pagano DA, Shelby MD
Natl. Inst. Environmental Health Sciences, Triangle Park, NC, 27709
Mutat Res; 100(1-4):67-70 1982

The mutagenic activity of 4-chloromethylbiphenyl (4CMB) was determined in Salmonella typhimurium strains TA1535, TA1537, TA98, and TA100 using the plate incorporation assay with and without rat-liver S9. 4CMB was positive in strains TA1537, TA98, and TA100 both with and without S9 activation. A weakly positive response was seen with strain TA1535 tested without activation. (4 Refs)

74. THE MUTAGENICITY OF 4CMB IN A MICROWELL BACTERIAL FLUCTUATION TEST.

Styles J, Pritchard N
Central Toxicology Lab., Imperial Chemical Industries Ltd., Macclesfield, Cheshire, England
Mutat Res; 100(1-4):71-73 1982

Microwell bacterial fluctuation test responses for 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) are described. 4CMB and BC were both positive in the presence or absence of S9 mix, although displacement of the dose-response curve was observed when S9 mix was used. 4HMB gave negative results with or without S9 mix. The results indicated that 4CMB is a direct-acting bacterial mutagen. (4 Refs)

75. MUTAGENICITY OF 4-CHLOROMETHYLBIPHENYL IN REPAIR-DEFICIENT STRAINS OF SALMONELLA TYPHIMURIUM.

Forster R
Water Res. Centre, Henley Road, Medmenham, Marlow, Bucks SL7 2HD, England
Mutat Res; 100(1-4):75-79 1982

The mutagenic activity of 4-chloromethylbiphenyl (4CMB) was examined in a series of repair deficient derivatives of Salmonella typhimurium LT2 using the fluctuation test. 4CMB was mutagenic to frameshift tester strains at 0.01-50 ug/ml, except in genetic backgrounds; no mutagenicity was observed in base-pair substitution tester strains at the dose levels used, except in the presence of the plasmid pKM101. Thus 4CMB appears to be primarily active as a frameshift mutagen. A much greater effect was seen in the excision-deficient strain TA1533 than in the repair wild-type strain D3052, suggesting that 4CMB forms an excisable DNA adduct. Increased cellular permeability resulting from the 'deep rough' (rfa) mutation led to greater mutation production by 4CMB, as can be seen by comparison of results for strains TA1533 and TA1538 which are isogenic except for the rfa mutation in TA1538. Strain TS27, which carries the recA allele and is completely deficient in recombination and error-prone repair, was almost as sensitive to 4CMB mutation as D3052; such a result suggests that a substantial proportion of the frameshift activity of 4CMB is independent of rec-lex function, consistent with the finding that the plasmid pKM101 has no observable effect on frameshift mutation by 4CMB and strains TA98 and TA1538 are equally sensitive to 4CMB mutation. The mechanism of 4CMB mutagenesis is discussed. (14 Refs)

76. AN ASSAY FOR MUTAGENIC ACTIVITY OF 4CMB, 4HMB AND BC, USING THE 'MICROTITRE' FLUCTUATION TEST.

Pour MS, Merrill C, Parry JM
Dept. Genetics, Univ. Coll. Swansea, Singleton Park, Swansea SA2 8PP, Wales
Mutat Res; 100(1-4):81-85 1982

The 'microtiter' bacterial fluctuation test was used to examine mutagenicity of 4-chloromethylbiphenyl, 4-hydroxymethylbiphenyl, and benzyl chloride in Salmonella typhimurium strains TA 98 and TA100; the strains are sensitive to frameshift and base-substitution mutagens, respectively. Only 4CMB was found to be a potent base-substitution and frameshift mutagen. (3 Refs)

77. FLUCTUATION TEST DATA ON 4-CHLOROMETHYLBIPHENYL (4CMB), 4-HYDROXYMETHYLBIPHENYL (4HMB) AND BENZYL CHLORIDE (BC) USING SALMONELLA TYPHIMURIUM TA98 AND TA100.

Sargent AW, Regnier AP
British Petroleum Res. Centre, British Petroleum Co. Ltd., Chertsey Road, Sunbury-on-Thames, Meddx. TW16 7LN, England
Mutat Res; 100(1-4):87-90 1982

Bacterial fluctuation tests were performed with and without metabolic activation using the Ames Salmonella typhimurium strains TA98 and TA100. The mutagenic potential of benzyl chloride, 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was assayed. 4CMB was mutagenic both with and without metabolic activation in TA100 and TA98. Data for 4HMB was negative. BC was non-mutagenic. (4 Refs)

78. UKEMS COLLABORATIVE GENOTOXICITY TRIAL. BACTERIAL MUTATION TESTS OF 4-CHLOROMETHYLBIPHENYL, 4-HYDROXYMETHYLBIPHENYL AND BENZYL CHLORIDE: ANALYSIS OF DATA FROM 17 LABORATORIES.

Venitt S
Pollards Wood Res. Station, Chester Beatty Res. Inst., Inst. Cancer Res., Nightingales Lane, Chalfont St. Giles, Bucks, HP8 4SP, England
Mutat Res; 100(1-4):91-109 1982

Results of bacterial mutagenicity assays of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) obtained by 17 laboratories are summarized and analyzed. Plate test, spontaneous mutation in plate tests, and fluctuation test data are reported. 4HMB was uniformly negative in plate tests using several strains of Salmonella typhimurium and one strain of Escherichia coli. In 183/206 plate tests, 4CMB produced positive dose-response curves, with slopes ranging from 0.01 to 57.9 mutants/ug. 4CMB was a potent, broad-spectrum mutagen, inducing mutations at frameshift loci (hisD3052 in TA1538 and TA98, and hisC3076 in TA1537) and base-pair substitution loci (hisG46 in TA1535 and TA100, and trpE ochre in E coli WP2uvrA(pKM101)). The only strains giving positive plate test results with BC were S typhimurium TA100 and E coli WP2uvrA(p). BC appears to be a base-pair substitution mutagen which does not require the addition of S9 for expression of mutagenic activity. Results from various laboratories were similar for plate tests. Plate and fluctuation test results are compared. (12 Refs)

79. THE INDUCTION OF DNA DAMAGE AND ITS REPAIR IN YEAST AFTER EXPOSURE TO 4CMB, BC AND 4HMB.

Tippins RS
Dept. Genetics, Univ. College Swansea, Singleton Park, Swansea SA2 8PP, Wales
Mutat Res; 100(1-4):119-122 1982

DNA-damaging abilities of 4-chloromethylbiphenyl (4CMB), benzyl chloride (BC), and 4-hydroxymethylbiphenyl (4HMB) in yeast were examined using a modification of the alkaline sucrose sedimentation technic. 4HMB did not induce DNA damage. 4CMB and BC induced comparable DNA damage. The yeast DNA-repair mechanisms appeared able to repair a greater percentage of BC-induced lesions than 4CMB-induced lesions after a repair-incubation period. (2 Refs)

80. THE TESTING OF 4CMB, 4HMB, AND BC FOR MUTAGENICITY IN A NEW NEUROSPORA CRASSA HETEROKARYON.

Luker MA
Inst. Animal Genetics, Edinburgh Univ., West Mains Road, Edinburgh EH9 3JN, Scotland
Mutat Res; 100(1-4):123-126 1982

Neither 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), nor benzyl chloride (BC) produced a dose response for mutation induction in the Neurospora crassa heterokaryon. The three compounds were therefore not mutagenic according to the test, although 4CMB, 4HMB, and BC did induce an increase in mutation frequency above control levels. Only the lower doses (150 ug/ml) of 4CMB and 4HMB in suspension treatments had any biological effect. Growing cells were more sensitive to 4CMB and 4HMB than were resting conidia, but 4HMB showed no mutagenic activity. Both BC and 4CMB produced dose-response data for ad+ and pFPA-R mutation induction and were regarded as mutagenic. (no Refs)

81. ASPERGILLUS NIDULANS AS A TEST ORGANISM FOR CHEMICAL MUTAGENS.

Igwe CN, Cohn P
Sch. Engineering and Science, Polytechnic Central London, 115 New Cavendish St., London W1R 8AL, England
Mutat Res; 100(1-4):127-131 1982

Effects of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) on survival, mitotic segregation, mitotic gene conversion, and point mutations in three strains of Aspergillus nidulans were studied. BC had the greatest effect and 4HMB the least on survival and gene conversion in a diploid strain and point mutation in a haploid strain. Neither 4CMB, 4HMB, nor BC had any effect on mitotic segregation. (4 Refs)

82. TESTING FOR MITOTIC CROSSING-OVER AND INDUCED ANEUPLOIDY USING ASPERGILLUS NIDULANS AS PART OF THE UKEMS TEST PROGRAMME.

Watkins P
Pharmaceuticals Div., Imperial Chemical Industries Ltd., Mereside, Alderly Park, Macclesfield, Cheshire SK10 4TG, England
Mutat Res; 100(1-4):133-138 1982

Abilities of 4-chloromethylbiphenyl (4CMB), benzyl chloride (BC), and 4-hydroxymethylbiphenyl (4HMB) to induce mitotic crossing-over in a diploid strain of Aspergillus nidulans (strain P), heterozygous for the gene determining resistance to p-fluorophenylalanine, were studied in selective media. 4CMB gave clear indication of the induction of crossing-over with increases over the length of the pre-incubation period. Inclusion of S9 mix reduced the effect. BC produced a small induction of crossing-over clearly noticeable only when the conidia were treated after 5 and 6 hr of incubation. 4HMB did not show any positive response in the assay. (4 Refs)

83. ASSAY OF THE INDUCTION OF MITOTIC CROSSING-OVER AND ANEUPLOIDY IN YEAST BY BC, 4CMB AND 4HMB.

Parry JM
Dept. Genetics, Univ. Coll. Swansea, Swansea SA2 8PP, Wales
Mutat Res; 100(1-4):139-143 1982

Abilities of benzyl chloride (BC), 4-chloromethylbiphenyl (4CMB), and 4-hydroxymethylbiphenyl (4HMB) to induce mitotic crossing-over and mitotic chromosome aneuploidy were assayed in strain D6 of Saccharomyces cerevisiae. Only BC and 4CMB produced mitotic crossing-over. Addition of S9 mix reduced the toxicity and genetic activity of both compounds. Neither 4CMB, 4HMB, nor BC induced mitotic chromosome aneuploidy. (3 Refs)

84. THE EFFECTS OF BC, 4CMB AND 4HMB UPON THE INDUCTION OF MITOTIC GENE CONVERSION IN YEAST.

Parry JM
Dept. Genetics, Univ. Coll. Swansea, Swansea SA2 8PP, Wales
Mutat Res; 100(1-4):145-151 1982

Effects of benzyl chloride (BC), 4-chloromethylbiphenyl (4CMB), and 4-hydroxymethylbiphenyl (4HMB) on mitotic gene conversion were studied in exponential phase cultures of the JD1 strain of Saccharomyces cerevisiae. Both BC and 4CMB induced mitotic gene conversion in the presence or absence of S9 mix. 4HMB showed no activity under comparable treatment conditions. S9 mix reduced the overall toxicity and genetic activity of both BC and 4CMB. 4CMB induced mitotic gene conversion in a manner directly related to cell toxicity, while BC showed a threshold effect. (3 Refs)

85. THE INDUCTION OF MITOTIC GENE CONVERSION IN THE YEAST, SACCHAROMYCES CEREVISIAE JD1 BY 4-CHLOROMETHYLBIPHENYL (4CMB), BENZYL CHLORIDE (BC) AND 4-HYDROXYMETHYLBIPHENYL (4HMB).

Brooks TM, Gonzalez LP
Sittingbourne Res. Centre, Shell Res. Ltd., Kent ME9 8AG, England
Mutat Res; 100(1-4):157-162 1982

Mitotic gene conversion induced by 4-chloromethylbiphenyl (4CMB), benzyl chloride (BC), and 4-hydroxymethylbiphenyl (4HMB) was scored in log-phase and stationary-phase cultures of Saccharomyces cerevisiae JD1. Both 4CMB and BC induced mitotic gene conversion, particularly in stationary-phase cells. 4HMB showed no activity in either of the assays. (2 Refs)

86. THE ACTIVITY OF 4CMB, 4HMB AND BC IN SACCHAROMYCES CEREVISIAE JD1.

Wilcox P, Parry JM
Dept. Genetics, Univ. Coll. Swansea, Singleton Park, Swansea SA2 8PP, West Glamorgan, Wales
Mutat Res; 100(1-4):163-168 1982

Abilities of benzyl chloride (BC), 4-chloromethylbiphenyl (4CMB), and 4-hydroxymethylbiphenyl (4HMB) to induce gene conversion in stationary phase cultures of the Saccharomyces cerevisiae strain JD1 were studied. Only 4CMB and BC induced mitotic gene conversion. At high viability levels 4CMB and BC showed comparable activities. However, as toxicity increased, BC showed much more potent convertogenic activity and 4CMB showed decreased gene conversion. Presence of S9 mix did not significantly affect the activity of any of the compounds. (2 Refs)

87. ACTIVITY OF 4-CHLOROMETHYLBIPHENYL, 4-HYDROXYMETHYLBIPHENYL AND BENZYL CHLORIDE IN ASSAYS FOR GENE CONVERSION AND PETITE INDUCTION IN SACCHAROMYCES CEREVISIAE STRAIN D4.

Mitchell IG, Gilbert PJ
Medicinal Res. Centre, Beecham Pharmaceuticals Res. Div., The Pinnacles, Harlow, Essex, England
Mutat Res; 100(1-4):169-172 1982

Gene conversion (GC) and petite induction (PI) in Saccharomyces cerevisiae strain D4 were assessed for their ability to correctly identify the carcinogenic and mutagenic potential of three chemical analogs: 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC). PI tests detected only the mutagenicity of BC and were highly variable. GC assays were highly reproducible and indicated the mutagenicity of 4CMB and lack of mutagenicity of 4HMB. GC assays failed to distinguish the potency of 4CMB from that of BC. (5 Refs)

88. MITOCHONDRIAL TOXICITY IN SACCHAROMYCES AS A MEASURE OF CARCINOGENICITY.

Patel R, Wilkie D
Dept. Botany and Microbiology, Univ. Coll., London, England
Mutat Res; 100(1-4):179-183 1982

Primary antimitochondrial activities of 4-chloromethylbiphenyl (4CMB), benzyl chloride, and 4-hydroxymethylbiphenyl (4HMB) were identified by selective inhibition of cell growth in non-fermentable medium, induction of the mitochondrial mutation petite, and selective blockage of mitochondrial protein synthesis. Only the biphenyls appeared to be carcinogenic based on their antimitochondrial activity; neither can be considered a potent carcinogen and 4CMB appears weaker than 4HMB. (2 Refs)

89. THE GENETIC TOXICOLOGY IN FUNGI OF 4-CHLOROMETHYLBIPHENYL (4CMB), 4-HYDROXYMETHYLBIPHENYL (4HMB) AND BENZYL CHLORIDE (BC). SURVEY OF THE RESULTS OF THE U.K.E.M.S. COLLABORATIVE GENOTOXICITY TRIAL 1981.

Parry JM, Wilcox P
Dept. Genetics, Univ. Coll. Swansea, Swansea SA2 8PP, Wales
Mutat Res; 100(1-4):185-200 1982

The genetic toxicology of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) has been studied in Saccharomyces cerevisiae, Aspergillus nidulans and Neuropsora crassa. Both 4CMB and BC are potent mutagens for nuclear genes in N crassa. No conclusions have been drawn about the abilities of any of the three compounds to induce point mutations in A nidulans. Both 4CMB and BC are potent inducers of mitotic gene conversion and mitotic crossing-over in fungi. 4CMB and BC are able to induce mitotic crossing-over in both yeast and A nidulans; no such activity has been detected with 4HMB. 4CMB has appeared to be a potent point mutagen in S cerevisiae. 4HMB is effective in inducing mitochondrial mutations and inhibiting the activity of mitochondrial genome. Results of studies on the effects of BC and 4CMB on the mitochondrial genome have been variable. Overall, the results of fungal assays have indicated that both 4CMB and BC are genetically active chemicals; no such activity has been detectable with 4HMB. (17 Refs)

90. TRANSFORMATION OF BHK 21 C13 CELLS BY BC, 4CMB, AND 4HMB USING THE METHOD OF STYLES.

Poole A, McGregor DB
Inveresk Res. International Ltd., Musselburgh, EH21 7UB, Scotland
Mutat Res; 100(1-4):215-217 1982

Cell-transforming potentials of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) were examined in baby hamster kidney cells growing without attachment in soft agar. 4HMB showed no evidence of cell-transforming potential, whereas 4CMB and BC may possess weak cell-transforming properties. The chemicals were scored as follows: 4HMB negative response, 4CMB unclear response, and BC weak positive response. (2 Refs)

91. A COMPARISON OF THE RESPONSE OF BHK21 C13 CELLS TO 4-CHLOROMETHYLBIPHENYL, 4-HYDROXYMETHYLBIPHENYL AND BENZYL CHLORIDE IN A CELL TRANSFORMATION TEST.

Dehnel JM, Daniel MR, Richold M
Dept. Mutagenesis, Huntingdon Res. Centre, Huntingdon, Cambridgeshire, PE18 6ES, England
Mutat Res; 100(1-4):223-226 1982

Baby hamster kidney 21 C13 cell anchorage-dependent growth, demonstrable as the formation of macroscopically visible colonies after seeding in soft agar, was used to determine the carcinogenic potentials of benzyl chloride (BC), 4-chloromethylbiphenyl (4CMB), and 4-hydroxymethylbiphenyl (4HMB). Transformation frequency and modification of supplementary criteria (dose-response relationship and doubling of number of transformed colonies in treated cultures compared to controls) were used as criteria of positive response. 4HMB satisfied all criteria for a positive response both in the presence and absence of metabolic activation. BC showed some evidence of transforming ability. The response of cells to 4CMB was inconsistent . (7 Refs)

92. THE ACTIVITY OF 4CMB IN THE BHK CELL-TRANSFORMATION ASSAY.

Styles J, Penman S
Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Park, Macclesfield, Cheshire SK10 4TJ, England
Mutat Res; 100(1-4):227-228 1982

The baby hamster kidney (BHK) transformation assay was used to study carcinogenic potential of 4-chloromethylbiphenyl (4CMB), benzyl chloride (BC), and 2-acetylaminofluorene (2AAF). A positive response was obtained with 4CMB and

2AAF but a negative result was observed with BC. The BHK assay demonstrated that 4CMB is a potent in vitro transforming agent in the absence of S9 mix. BC, a known carcinogen, was negative in the assay, suggesting that 4CMB and BC were tested in a system where the conditions of the test did not reflect those in vivo. (6 Refs)

93. ENHANCEMENT OF VIRAL TRANSFORMATION OF HAMSTER EMBRYO CELLS BY PRETREATMENT WITH 4-CHLOROMETHYLBIPHENYL.

Hatch GG, Mamay PD
Northrop Services, Research Triangle Park, NC
Mutat Res; 100(1-4):229-233 1982

Effects of two-fold chemical dilutions of 4-chloromethylbiphenyl (4CMB) extending over a 33-fold range were used to determine enhancement of viral transformation in Syrian hamster embryo cells. The highest 4CMB concentration (50 ug/ml) produced significant toxicity (62% survival). Lower doses had no significant cytotoxic effect. Chemical pretreatment with 4CMB enhanced the viral transformation frequency in a concentration-dependent manner. The two highest treatment concentrations (50 and 25.0 ug/ml) produced significantly increased enhancement ratios (2.8 and 1.5, respectively). A large absolute increase in viral foci was seen at both 50 and 25 ug/ml 4CMB. The results suggest that 4CMB has carcinogenic potential. (16 Refs)

94. CYTOTOXIC AND MUTAGENIC EFFECTS AT THE HGPRT LOCUS OF 4CMB IN V79 CHINESE HAMSTER CELLS.

Fox M
Paterson Lab., Christie Hosp., Manchester M20 9BX, England
Mutat Res; 100(1-4):235-238 1982

Cytotoxic and mutagenic effects of 4-chloromethylbiphenyl (4CMB) at the HGPRT locus were assayed in V79 Chinese hamster cells. The spontaneous mutant frequency was significantly higher when 8-azaguanine (AZ) was used for selection than when 6-thioguanine (TG) was used. When 4CMB-treated cells were plated with AZ, an absolute increase in numbers of AZ-resistant colonies was observed at each expression time when cells were exposed to 4CMB doses between 30 and 60 ug/ml. Further increase in dose to 70 ug/ml resulted in a marked fall in number of colonies recovered. Data obtained using TG for selection were more variable due to the lower numbers of colonies scored, and a reproducible increment in actual number of colonies was not obtained at all expression times. The pooled data indicated some increase in induced mutant frequencies after exposure to 4CMB concentrations of 30 ug/ml or higher. The data indicated a weak positive response irrespective of AZ or TG selection. A possible threshold on the dose-response curve for induced mutation could differentiate 4CMB from direct-acting alkylating agents and UV light. (2 Refs)

95. THE CYTOTOXIC AND MUTAGENIC EFFECTS OF 4CMB, BC, AND 4HMB IN V79 CHINESE HAMSTER CELLS.

Mirzayans F, Davies PJ, Parry JM
Dept. Genetics, Univ. Coll. Swansea, Singleton Park, Swansea SA2 8PP, Wales
Mutat Res; 100(1-4):239-244 1982

The cytotoxicity and mutagenicity of 4-chloromethylbiphenyl (4CMB), benzyl chloride (BC), and 4-hydroxymethylbiphenyl (4HMB) were measured in V79 Chinese hamster cells. BC and 4CMB each produced mutations at the V79 HGPRT locus; BC having a greater mutagenic activity than 4CMB at equivalent toxic doses. No mutagenic activity was found for 4HMB. Although both BC and 4CMB produced mutations at 6-thioguanine- and ouabain-sensitive loci, colony numbers were insufficient to draw any conclusions regarding the loci. (2 Refs)

96. EFFECT OF BC, 4CMB AND 4HMB ON THE MUTATION OF V79 CELLS TO AZAGUANINE RESISTANCE.

Lee CG, Webber TD
Chemical Defence Establishment, Porton Down, Salisbury, Wilts., England
Mutat Res; 100(1-4):245-248 1982

Conversion of 8-azaguanine (AG)-sensitive V79 Chinese hamster cells to AG-resistant cells was used to assay the mutagenicity of benzyl chloride (BC), 4-chloromethylbiphenyl (4CMB), and 4-hydroxymethylbiphenyl (4HMB). Cytotoxic and mutagenic results were positive for BC and 4CMB. Results for 4HMB were considered negative; cell response to 4HMB was erratic. (no Refs)

97. THE EFFECTS OF 4CMB, 4HMB, AND BC ON SCE, CHROMOSOME ABERRATION AND POINT MUTATION IN CULTURED CHINESE HAMSTER OVARY CELLS.

Phillips BJ, James TE
British Industrial Biological Res. Assoc., Woodmansterne Road, Carshalton, Surrey SM5 4DS, England
Mutat Res; 100(1-4):263-269 1982

Mutagenicity of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was studied in vitro in Chinese hamster ovary (CHO-KI-BH4) cells in the absence of exogenous metabolic activation systems. CHO-KI-BH4 cells were exposed to 4CMB, 4HMB, or BC for 2 hr. Tests of relative plating efficiency indicated that 4HMB is nontoxic at concentrations up to 100 ug/ml; above 100 ug/ml 4HMB precipitated from soln. 4CMB was slightly more toxic than BC. Sister chromatid exchanges (SCE) were significantly increased by BC in a dose-related manner; the max effect of 4CMB was a doubling of the background frequency of SCE at a concentration of 7 ug 4CMB/ml; 4HMB had no effect on the frequency of SCE. 4CMB produced moderate but significant chromosomal aberrations (CA) within a concentration range of 10-20 ug/ml; BC produced somewhat more CA but at higher doses than 4CMB. 4HMB produced no effect on CA. 4CMB produced a slight increase in the frequency of cell mutations (CM) within a narrow range of doses around 10 ug/ml, BC produced a small increase at a dose of 18 ug/ml, and 4HMB had no effect on CM. Results indicate that 4CMB and BC are weakly mutagenic in the absence of an exogenous metabolic activation system. SCE, CA, and CM test results agreed quantitatively and qualitatively. (4 Refs)

98. THE USE OF CULTURED MAMMALIAN CELLS IN THE UKEMS COLLABORATIVE GENOTOXICITY TRIAL (1981).

Arlett CF
MRC Cell Mutation Unit, Univ. Sussex, Falmer, Brighton BN1 9QG, East Sussex, England
Mutat Res; 100(1-4):271-276 1982

Genotoxicity trials of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4-HMB), and benzyl chloride (BC) are reviewed. The trials used cultures of cells from the mouse (cell line C3H/10T1/2 and lymphoma lines P388 and L5178Y), Chinese hamster (V79 male lung cells and ovary cells), and man (HeLa cells). Mutation test consistently indicated that 4CMB is mutagenic in the presence or absence of S9 mix. No mutagenic activity was found for 4HMB. BC was mutagenic in 3/4 studies, but the activity of BC could not be scaled to that of 4CMB. CMB was not mutagenic in the ouabain system, suggesting that 4CMB does not act as a frame-shift mutagen in mammalian cells. Studies of cell transformation produced conflicting results, particularly with the BHK transformation assay. DNA repair studies indicate that 4CMB is genotoxic while 4HMB is not. Contradictory results were reported for BC. Positive indications of mutagenicity were found in 17/26 tests of 4CMB, 2/16 tests of 4HMB, and 8/17 tests of BC. Results suggest that 4CMB is mutagenic while 4HMB is not; more studies are required to determine the mutagenicity of BC. (17 Refs)

99. MUTATION AT THE TK LOCUS OF MOUSE LYMPHOMA L5178Y CELLS BY 4CMB, 4HMB AND BC.

Ross CA, McGregor DB
Inveresk Res. International Ltd., Musselburgh, EH21 7UB, Scotland
Mutat Res; 100(1-4):249-251 1982

Mutation at the thymidine kinase locus of mouse lymphoma L5178Y cells was used to assay mutagenicity of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4-HMB), and benzyl chloride (BC). In the presence of S9 mix none of the compounds produced increased mutation relative to controls. Without S9 mix only 4CBM had significant mutagenicity. (1 Ref)

100. THE INDUCTION OF MUTANTS IN L5178Y MOUSE LYMPHOMA CELLS BY 4-CHLOROMETHYLBIPHENYL.

Arlett CF, Muriel WJ, Cole J, Lowe J
MRC Cell Mutation Unit, Univ. Sussex, Falmer, Brighton, Sussex BN1 9QG, England
Mutat Res; 100(1-4):253-256 1982

The mutagenicity of 4-chloromethylbiphenyl (4CMB) was assessed in L5178Y mouse lymphoma cells by measuring the appearance of mutant cells resistant to various metabolic inhibitors. At a concentration of 50 ug/ml, 4CMB produced significant dose-dependent induction of resistance to methotrexate and 1-beta-D-arabinofuranosylcytosine; induction of resistance to 6-thioguanine was dose-related but not significant. 4CMB was not mutagenic with respect to ouabain resistance. (6 Refs)

101. STUDIES WITH 4-CHLOROMETHYLBIPHENYL IN P388 CELLS SELECTED IN 5-IODO-2'-DEOXYURIDINE.

Anderson D, Cross MF
Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Park, Nr. Macclesfield, Cheshire, England
Mutat Res; 100(1-4):257-261 1982

The mutagenicity of 4-chloromethylbiphenyl (4CMB) was tested in P388 mouse lymphoma cells grown in the presence of 5-iodo-2'-deoxyuridine. Methyl methanesulfonate and benzo[a]pyrene were used as positive controls. 4CMB was mutagenic with or without S9 mix. With S9 mix, toxicity was lower with 60-min exposure than with 30-min exposure. Reduced toxicity may have resulted from detoxification of 4CMB by the S9 mix. (6 Refs)

102. CHROMOSOME ANALYSIS OF CULTURED RAT-LIVER EPITHELIAL CELLS (RL4) TREATED WITH 4-CHLOROMETHYLBIPHENYL, 4-HYDROXYMETHYLBIPHENYL AND BENZYL CHLORIDE.

Malallah G, Danford N, Parry JM
Genetic Toxicology Group, Univ. Coll. Swansea, Swansea SA2 8PP, Wales
Mutat Res; 100(1-4):279-282 1982

Induction of chromosomal aberrations by 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was studied in rat-liver epithelial cells of the line RL4, which retains some metabolic activation. Cytotoxicity was determined by seeding 50,000 cells/well onto culture plates, culturing for 24 hr, and then exposing the cells to a test chemical for 24 hr. The concentration of test chemical producing 50% inhibition of cell growth (GI50) was calculated for each chemical. Genotoxicity assays were conducted using 25, 50, 75, and 100% of the GI50. Cell cultures were exposed for 24 hr to 6, 12, 18, or 24 ug 4CMB/ml, 25, 50, 75, or 100 ug 4HMB/ml, or 7.5, 15, 22.5, or 30 ug BC/ml. Both 4CMB and BC produced significant increases in chromosomal aberrations at doses that were only slightly toxic to RL4 cells. Sixty uM 4CMB produced approx 6x as much damage as 60 uM BC; 120 uM 4CMB produced greater than 10x as much damage as 120 uM BC. 4CMB produced 3x as much chromosome damage as equitoxic concentrations of BC. No clear effects on chromosome number were noted, except an increase in the number of cells with 43 or fewer chromosomes at 18 or 24 ug/ml 4CMB. Since no increase was observed in the number of cells with 46 or more chromosomes, 4CMB apparently does not cause nondisjunction. 4HMB produced no chromosomal aberrations. Results indicate that 4CMB and BC are clastogenic and 4CMB has the greater activity. (1 Ref)

103. DNA DAMAGE AND ITS REPAIR IN CULTURED HUMAN ALVEOLAR TUMOR CELLS TREATED WITH BENZYL CHLORIDE, 4-CHLOROMETHYLBIPHENYL OR 4-HYDROXYMETHYLBIPHENYL.

Mirzayans R, Meredith J, Waters R
Dept. Genetics, Univ. Coll. Swansea, Singleton Park, Swansea SA2 8PP, Wales
Mutat Res; 100(1-4):203-206 1982

Cultured human alveolar A549 tumor cells were treated with various doses of benzyl chloride (BC), 4-chloromethylbiphenyl (4CMB), and 4-hydroxymethylbiphenyl (4HMB) for 4 hr; either inhibition of cell growth or DNA damage and its repair were examined. Both BC and 4CMB induced DNA damage. Although 4CMB was approx 5x more active at the same dose, but equitoxic doses resulted in the same rates of DNA repair after cytarabine incorporation. BC also induced repairable single-strand breaks at a low frequency. 4HMB, although lethal to the cells, did not induce any detectable DNA damage. (2 Refs)

104. UKEMS TRIAL COMPOUNDS: INDUCTION OF UNSCHEDULED DNA SYNTHESIS IN HELA S3 CELLS.

Barrett RH
Res. Dept., Boots Co. Ltd., Pennyfoot St., Nottingham NG2 3AA, England
Mutat Res; 100(1-4):207-209 1982

Significant increases in unscheduled DNA synthesis (UDS) in HeLa S3 cells were induced at 4-chloromethylbiphenyl (4CMB) dose levels of 10(-4) and 10(-5) M in the absence and 10(-5) M in the presence of S9 mix. 4-Hydroxymethylbiphenyl (4HMB) showed no evidence of UDS induction at dose levels up to 10(-3) M; cytotoxicity was evident at this concentration. BC slightly elevated UDS at 10(-4) M in the absence of S9 mix. The results indicated carcinogenicity of 4CMB and 4HMB but did not agree with previous findings on tumorigenicity of BC in rats. (9 Refs)

105. AN INVESTIGATION OF DNA-REPAIR PHENOMENA INDUCED BY 4-CHLOROMETHYLBIPHENYL (4CMB).

Pearson CM, Edwards K
Central Toxicology Lab., Imperial Chemical Industries, Alderley Park, Macclesfield, Cheshire, England
Mutat Res; 100(1-4):211-214 1982

Ability of 4-chloromethylbiphenyl (4CMB) to induce phenomena associated with DNA damage and its repair were studied in cultured HeLa cells with assays of strand breakage, unscheduled DNA synthesis (UDS), and repair replication. A dose-related positive effect was observed for strand breaks, with 250 ug/ml showing a significant amount of 3H-DNA loss from the filter. The assays of UDS or repair replication showed no increase in thymidine incorporation above control levels and therefore no repair synthesis. Repair replication at doses of 100 ug/ml 4CMB exhibited an inhibition of thymidine incorporation into DNA compared to controls. (3 Refs)

106. AN ASSESSMENT OF THE CLASTOGENIC POTENTIAL OF 4-CHLOROMETHYLBIPHENYL IN HUMAN LYMPHOCYTES IN VITRO.

Richardson CR, Wildgoose J
Central Toxicology Lab., Genetic Toxicology Section, Imperial Chemical Industries Ltd., Alderley Park, Macclesfield, Cheshire, England
Mutat Res; 100(1-4):287-293 1982

Clastogenicity of 4-chloromethylbiphenyl (4CMB) was studied in vitro in lymphocytes from four human donors. The lymphocytes were stimulated by phytohemagglutinin. 4CMB produced genetic damage in cells from 3/4 donors according to one criterion and in cells from 1/4 donors according to a second criterion. The most common defects produced were chromatid and chromosome gaps. Results indicate that 4CMB is clastogenic but only at concentrations that are cytotoxic. (3 Refs)

107. METAPHASE ANALYSIS OF HUMAN LYMPHOCYTES TREATED WITH 4-CHLOROMETHYLBIPHENYL AND BENZYL CHLORIDE.

Kirkland DJ, Smith KL, Jenkinson PC
Toxicol Lab. Ltd., Bromyard Road, Ledbury, Herefordshire, HR8 1LG, England
Mutat Res; 100(1-4):297-299 1982

Chromosome mutagenicity of 4-chloromethylbiphenyl (4CMB) and benzyl chloride (BC) was assayed in lymphocytes from a healthy human donor. Mitosis was inhibited by 4CMB at concentrations greater than 20 ug/ml and by BC at concentrations greater than 10 ug/ml. At lower concentrations neither compound increased the number of cells showing chromosome breaks or the number of breaks/cell. 4CMB increased gaps at 10 ug/ml. Results indicate that neither 4CMB nor BC is mutagenic in human lymphocytes. (2 Refs)

108. SISTER-CHROMATID EXCHANGES IN HUMAN LYMPHOCYTES TREATED WITH 4-CHLOROMETHYLBIPHENYL AND BENZYL CHLORIDE.

Kirkland DJ, Jenkinson PC, Smith KL
Toxicol Lab. Ltd., Bromyard Road, Ledbury, Herefordshire, HR8 1LG, England
Mutat Res; 100(1-4):301-304 1982

Induction of sister chromatid exchanges (SCE) in human lymphocytes by exposure to noninhibitory doses of 4-chloromethylbiphenyl (4CMB) and benzyl chloride (BC) was studied. 4CMB produced significant increases in frequency of SCE. BC produced increases that were just barely significant. Results suggest that SCE assay may be a more accurate test of mutagenicity in human lymphocytes than chromosome breakage assay. (3 Refs)

109. DROSOPHILA, SEX-LINKED RECESSIVE LETHAL TESTS WITH 4-CHLOROMETHYLBIPHENYL AND BENZYL CHLORIDE.

MacDonald D, Telford K
Inst. Animal Genetics, West Mains Road, Edinburgh EH9 3JN, Scotland
Mutat Res; 100(1-4):335-338 1982

Mutagenicity of 4-chloromethylbiphenyl (4CMB) and benzyl chloride (BC) was studied in male Drosophila melanogaster. Larva were exposed to 4CMB or BC by feeding. Adults were exposed to 4CMB by feeding or by intra-abdominal injection. Males were then mated with females, and offspring were examined for sex-linked recessive lethal mutations. Neither 4CMB nor BC showed any significant toxicity or mutagenicity when given in doses of 5-660 ug. (1 Ref)

110. GENETIC ACTIVITIES OF 4-CHLOROMETHYLBIPHENYL, THE 4-HYDROXY DERIVATIVE AND BENZYL CHLORIDE IN THE SOMA AND GERM LINE OF DROSOPHILA MELANOGASTER.

Fahmy MJ, Fahmy OG
Dept. Genetics, Inst. Cancer Res., Pollard Woods Res. Station, Chalfont St. Giles, Buckinghamshire HP8 4SP, England
Mutat Res; 100(1-4):339-344 1982

Induction of alterations in gene expression by 4-chloromethylbiphenyl (CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was studied in the soma and germ line of Drosophila melanogaster. Late embryos and newly hatched larvae were exposed to the test compounds in concentrations up to 2 milliM (mM) until maturation. Somatic alterations were measured by determining alterations in expression of the unstable w+ locus in mature treated males. At 0.5-2.0 mM, 4CMB, 4HMB, and BC increased the frequency of red eye sectors resulting from repression or deletion of the zeste-regulatory proximal subunits of the w+ locus. 4CMB and 4HMB had approx the same activity, while BC had an activity approx twice that of the other two compounds. At 0.5-2.0 mM concentrations 4HMB and BC each increased the frequency of occurrence of white eye sectors resulting from deletions within the structure of the w+ locus by approx one order of magnitude relative to untreated controls. 4CMB did not affect the occurrence of white sectors. Red sectors had a mean size of 27 +-6 ommatidia, corresponding to an eye anlage size of approx 30 cells at the time of induction. White sectors had a mean size of 87 +-17 ommatidia, corresponding to an eye anlage size of 9 cells at the time of induction. These findings indicate that induction of red sector occurred at or after the time of genetic determination during eye differentiation. The test compounds are apparently weak mutagens in the order 4CMB less than or equal to 4HMB less than or equal to BC. (5 Refs)

111. THE ASSAY OF 4-CHLOROMETHYLBIPHENYL IN THE DOMINANT LETHAL ASSAY IN MICE.

Wickramaratne GA, Richards D, Kilmartin M, Keetch D
Central Toxicology Lab., ICI Ltd., Alderley Park, Macclesfield, Cheshire SK10 4TJ, England
Mutat Res; 100(1-4):351-352 1982

Mutagenicity of 4-chloromethylbiphenyl (4CMB) was studied in an assay of dominant lethal mutation in Swiss Albino Alderley Park mice. Male mice received 4CMB po for 5 days and were then mated. Examination of uterine contents of females showed an increased in the number of early deaths per pregnancy only when the positive control substance, ethyl methanesulfonate, was used. 4CMB did not produce positive results. (1 Ref)

112. 4CMB, 4HMB, AND BC EVALUATED BY THE MICRONUCLEUS TEST USING A MULTIPLE SAMPLING METHOD.

Holmstrom M, McGregor DB, Willins MJ, Cuthbert JA, Carr S
Inveresk Res. International Ltd., Musselburgh, EH21 7UB, Scotland
Mutat Res; 100(1-4):357-359 1982

Mutagenicity of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was measured in vivo in CD-1 male mice. Mice received test compounds po at various fractions of the LD50. The frequency of formation of micronuclei in polychromatic erythrocytes was determined at different sampling times. No mutagenicity was indicated for any of the test compounds by this method. (5 Refs)

113. 4CMB: INVESTIGATION OF ACTIVITY IN A MOUSE MICRONUCLEUS TEST.

Whalley HE, Bootman J, Rees R
Life Science Res., Stock, Essex, England
Mutat Res; 100(1-4):361-364 1982

Mutagenic effects of 4-chloromethylbiphenyl (4CMB) were studied in vivo in CD-1 mice. 4CMB was injected ip daily for 5 days at doses up to lethal levels. Toxicity of 4CMB was greater in females than in males. 4CMB produced no increase in the occurrence of micronuclei of polychromatic erythrocytes relative to controls. Results indicate no mutagenicity for 4CMB identifiable by this method. (2 Refs)

114. ASSAY OF 4CMB, 4HMB, AND BC BY THE MICRONUCLEUS TEST: SUBCUTANEOUS ADMINISTRATION.

Scott K, Topham JC
Imperial Chemicals Ltd., Mereside, Alderley Park, Macclesfield, Cheshire, England
Mutat Res; 100(1-4):365-371 1982

In vivo mutagenicity of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was studied in (CBA x Balb/c)F1 mice. Test compounds were injected sc in doses up to the max tolerated dose of 4CMB and 4HMB and up to 2,000 mg/kg BC. None of the test compounds produced any increase in frequency of micronuclei in polychromatic erythrocytes. No mutagenicity was detected by this method. (2 Refs)

115. CYTOGENETIC EFFECTS OF BC AND 4CMB IN THE MOUSE EVALUATED BY THE MICRONUCLEUS TEST.

Hartley-Asp B
Pharmacology Dept., AB Leo Res. Lab., Box 941, S-251 09 Helsingborg, Sweden
Mutat Res; 100(1-4):373-374 1982

In vivo mutagenicity of 4-chloromethylbiphenyl (4CMB) and benzyl chloride (BC) was measured in SPF NMRI female mice using the micronucleus assay. Various doses of the test compounds were injected ip in two fractions. 4CMB was 10x as toxic as BC in test animals. Neither compound increased the frequency of micronuclei in polychromatic erythrocytes. (no Refs)

116. AN EVALUATION OF THE MUTAGENIC POTENTIAL OF 4-CHLOROMETHYLBIPHENYL (4CMB) USING THE MICRONUCLEUS TEST.

Richardson JC, Proudlock RJ, Richold M
Dept. Mutagenesis, Huntingdon Res. Centre, Huntingdon, Cambridgeshire, PE18 6ES, England
Mutat Res; 100(1-4):375-378 1982

In vivo mutagenicity of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was measured in COBS CD-1 (ICR) BR (ICR derived) mice. Test compounds were injected ip. None of the compounds produced any increase in frequency of micronuclei in polychromatic RBC. The highest dose of 4CMB did not affect the ratio normochromatic/polychromatic RBC. (10 Refs)

117. IS 4CMB CLASTOGENIC IN VIVO? PRELIMINARY RESULTS FROM THE MOUSE TRANSPLACENTAL MICRONUCLEUS TEST.

Cole RJ, Cole J
Biology Div., Sussex Centre Medical Res., Univ. Sussex, Brighton, England
Mutat Res; 100(1-4):379-380 1982

In vivo mutagenicity of 4-chloromethylbiphenyl (4CMB) was tested by a transplacental micronucleus assay in 'Porton' strain albino mice. 4CMB was injected ip at 0-250 mg/kg into pregnant mice on day 16 or 17 of pregnancy. Polychromatic RBC from fetal liver and neonatal mice were examined. 4CMB was highly toxic to fetuses but was not clastogenic. (2 Refs)

118. ACTIVITY OF 4CMB IN THE MOUSE-SKIN SEBACEOUS-GLAND SUPPRESSION TEST.

Ashby J, Longstaff E
Central Toxicology Lab., Imperial Chemical Industries Ltd., Macclesfield, Cheshire, England
Mutat Res; 100(1-4):391-393 1982

Suppression of sebaceous glands by 4-chloromethylbiphenyl (4CMB) was studied in Alderley Park strain Swiss mice. 4CMB was applied directly to the skin 0-16 mg/ml 2x/day for 3 days. Benz[a]pyrene was used as a positive control. 4CMB produced a significant reduction in incidence of sebaceous glands in treated skin samples. The reduction may be due to potential carcinogenicity or to a direct irritant effect. (7 Refs)

119. EVALUATION OF 4CMB IN THE SUBCUTANEOUS IMPLANT TEST.

Longstaff E, Gaunt C
Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Park, Macclesfield, Cheshire, England
Mutat Res; 100(1-4):395-397 1982

Carcinogenicity of 4-chloromethylbiphenyl (4CMB) was studied by means of sc implant in Alderley Park strain mice. 4CMB was absorbed onto millipore filters which were then implanted in the dorso-lumbar region of the mice. A positive control substance, benzo[a]pyrene, had a significant carcinogenic effect. No significant carcinogenic effect was found for 4CMB, although significant fibrosis and some edema were produced. (5 Refs)

120. CARCINOGENICITY BIOASSAY OF 4-CHLOROMETHYLBIPHENYL (4CMB), 4-HYDROXYMETHYLBIPHENYL (4HMB) AND BENZYL CHLORIDE (BC) ON MOUSE SKIN: INTERIM (7 MONTH) REPORT.

Ashby J, Gaunt C, Robinson M
Central Toxicology Lab., Imperial Chemical Industries Ltd., Alderley Edge, Macclesfield, Cheshire, England
Mutat Res; 100(1-4):399-401 1982

Carcinogenic potential of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was studied in Alderley Park Swiss mice. Test chemicals were applied at 100 ug 2x/wk in a continuing study. Benzo[a]pyrene (BP), a positive control, produced squamous cell carcinoma of the skin within 5 mo. Initial results indicate that 4CMB, 4HMB, and BC are less carcinogenic than BP, although insufficient time has elapsed to conclude that the compounds are noncarcinogenic. (no Refs)

121. ATTEMPTS TO INITIATE SKIN TUMOURS IN MICE IN THE 2-STAGE SYSTEM USING 4-CHLOROMETHYLBIPHENYL (4CMB), 4-HYDROXYMETHYLBIPHENYL (4HMB), AND BENZYL CHLORIDE (BC): REPORT OF THE EXPERIMENT AT 10 MONTHS.

Coombs MM
Chemistry Lab., Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX , England
Mutat Res; 100(1-4):403-405 1982

Carcinogenicity of 4-chloromethylbiphenyl (4CMB), 4-hydroxymethylbiphenyl (4HMB), and benzyl chloride (BC) was studied in Theiler's Original strain mice. Test compounds were applied to the skin in single doses of 1 mg. After 1 wk, and 2x/wk thereafter, croton oil was applied as a tumor promoter. Interim results indicate that 4CMB, 4HMB, and BC are not strong skin carcinogens. Further time is required to confirm weak carcinogenicity of 4CMB and 4HMB. (2 Refs)

DRUGS, COSMETICS, DETERGENTS AND OTHER COMMERCIAL MATERIALS

122. RETINOL (VITAMIN A) INHIBITS SISTER CHROMATID EXCHANGES AND CELL CYCLE DELAY INDUCED BY CYCLOPHOSPHAMIDE AND AFLATOXIN B1 IN CHINESE HAMSTER V79 CELLS.

Huang CC, Hsueh JL, Chen HH, Batt TR
Dept. Experimental Biology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Carcinogenesis; 3(1):1-5 1982

Retinol (vitamin A alcohol) at the doses tested neither induced an increase of frequency of sister chromatid exchanges (SCE) nor cell cycle delay in Chinese hamster V79 cells with or without the metabolic activation of S-9 mix. However, it inhibited SCE frequencies and cell cycle delay in V79 cells induced by the indirect mutagen cyclophosphamide or aflatoxin B1. The inhibition was found to be dose and time dependent. These results suggest that retinol itself may have no direct effect on the genetic materials but rather exert its effects possibly by inhibiting the metabolic activation of an indirect mutagen or carcinogen. Thus, the antitumor activities of retinoids may not be limited to the widely accepted role of the preventing the promotion step but also the initiation step of carcinogenesis. (Author abstract) (33 Refs)

123. MUTAGENICITY OF RUBBER VULCANIZATION GASES IN SALMONELLA TYPHIMURIUM.

Hedenstedt A, Ramel C, Wachtmeister CA
Wallenberg Lab., Univ. Stockholm, S-106-91 Stockholm, Sweden
J Toxicol Environ Health; 8(5/6):805-814 1981

The effect of changes in stock composition and thermal treatment of vulcanization gases was investigated by means of short term mutagenicity tests. Vulcanization fumes from a styrene-butadiene rubber produced a significant increase in mutations when compared to control tests. Pyrolysis gases from a peroxide cured butadiene acrylonitrile rubber had no mutagenic effect, but were markedly more toxic than the other polymers tested. Magnesium oxide cured chloroprene rubber had a direct mutagenic effect. Sulfur and peroxide cured ethylene propylene rubbers both showed a mutagenic effect. Temperature apparently affects the type of compound released and the resulting mutagenicity. (18 Refs)

124. REACTIONS OF VINYL CHLORIDE WITH RNA AND DNA OF VARIOUS MOUSE TISSUES IN VIVO.

Bergman K
Toxicology Lab., Natl. Food Admin., Box 622, S-751 26 Uppsala, Sweden
Arch Toxicol; 49(2):117-129 1982

The irreversible binding of 14C-vinyl chloride metabolites to RNA and DNA of mouse brain, lung, liver, kidney, spleen, pancreas, and testes after a single ip injection has been studied. Hydrolysates of nucleic acids from selected organs were separated on Aminex A6 for quantitation of alkylation products. Radioactivity in nucleic acids was registered in all of the studied organs with the exception of brain. RNA from spleen, pancreas and liver, and DNA from spleen and liver contained the highest amounts of radioactivity. In nucleic acids from spleen and pancreas, both organs of high metabolic activity, the entire radioactivity was found metabolically incorporated as C1-fragments. In RNA of kidney and liver, a large part of the radioactivity was also present as incorporated C1-fragments, but 3,N4-ethenocytidine (in kidney) as well as 1,N6-ethenoadenosine and 1,N6-ethenoadenine (in kidney and liver) were identified as alkylation products. In liver DNA, incorporation of C1-fragments was insignificant, indicating different interactions of vinyl chloride metabolites (C1-fragments and alkylating products) with RNA and DNA. The elution profiles of radioactivity in hydrolysates of liver DNA were dominated by an alkylation product of unknown structure (probably a derivative of deoxyguanosine). Possibly, 1,N6-ethenodeoxyadenosine and 1,N6-ethenoadenine were also present in liver DNA. The results are consistent with the ability of viny chloride to act as a multipotent carcinogen by alkylation of DNA in several tissues. (Author abstract) (45 Refs)

125. DNA DAMAGE INDUCED BY THE ANTIHISTAMINIC DRUG METHAPYRILENE HYDROCHLORIDE.

Althaus FR, Lawrence SD, Sattler GL, Pitot HC

McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706

Mutat Res; 103(3-6):213-218 1982

Methapyrilene hydrochloride (MH) added to the medium stimulated DNA-repair synthesis in cultured hepatocytes from adult male Holtzman rats. The effect was dose dependent over the range 10(-2)-10(-6) M, with a peak at 10(-3) M. Of more than 30 compounds tested by this protocol only known carcinogens and UV irradiation have been shown to produce more DNA damage than MH. MH treatment of hepatocytes for 30, 90, and 180 min clearly decreased the sedimentation velocity of hepatocellular DNA on alkaline sucrose gradients, indicating the formation of alkaline-labile lesions. The present evidence, when considered in light of recent studies demonstrating the tumor-inducing ability of MH in rats lead to the conclusion the MH is a complete carcinogen. (10 Refs)

126. METHAPYRILENE EFFECTS ON INITIATION AND PROMOTION OF GAMMA-GLUTAMYL-TRANSPEPTIDASE POSITIVE FOCI IN RAT LIVER.

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Div. Toxicology, Dept. Pharmacology, Coll. Medicine, Ohio State Univ., Columbus, OH, 43210

Res Commun Chem Pathol Pharmacol; 35(1):51-61 1982

The initiating and promoting effects of methapyrilene were evaluated using the hepatic enzyme-altered foci bioassay. Male Sprague-Dawley rats were partially hepatectomized and 24 hr later were administered either methapyrilene or nitrosodiethylamine by oral gavage. Subsequently, the animals were promoted with 500 ppm phenobarbital or 200 ppm methapyrilene in drinking water for 8 wk. Fresh frozen sections of liver were then stained and scored for gamma-glutamyl-transpeptidase (GGT)-positive foci. Methapyrilene, when tested as the nominal initiator at a single dose of 50 mg/kg or at two doses of 130 mg/kg and promoted by phenobarbital, did not induce foci above background levels. However, when substituted for phenobarbital as the promoting agent following nitrosodiethylamine initiation, methapyrilene enhanced enzyme-altered foci formation to an equal or greater extent than did the promoter phenobarbital. These results suggest that the carcinogenic effects of methapyrilene may be related to its ability to enhance hepatic tumorigenesis. (Author abstract) (19 Refs)

127. MUTAGENICITY OF THE ANTIPARASITIC DRUG VERMOX FOR SALMONELLA TYPHIMURIUM HISTESTER STRAINS.

Paulikova H, Dobias L

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Mutat Res; 90(4):463-468 1981

Salmonella typhimurium strains TA100, TA98, TA1535, and TA 1538 were exposed to Vermox to test the mutagenicity (MG) of methyl-5(6)-benzoyl-2-benzimidazole carbamate, a component of Vermox. No MG as indicated by histidine prototrophic reversion was noted with or without metabolic activation by rat liver S9. Blood samples from rats treated with Vermox did not produce an increase in reversions, indicating that metabolic activation in vivo does not produce mutagenic activity. (11 Refs)

128. LUNG CARCINOGENESIS BY PROCARBAZINE CHLORATE IN BALB/C MICE.

Bacci M, Cavaliere A, Fratini D

Inst. Pathological Anatomy and Histology, Perugia Univ., P.O. Box 54, 06100 Perugia, Italy

Carcinogenesis; 3(1):71-73 1982

A study of the carcinogenic action of procarbazine chlorate in BALB/c/Cb/Se mice showed that this substance significantly increases the incidence of lung tumors in both sexes. The induced tumors were alveolar-lining, papillary and alveolar-papillary type carcinomas with a tendency to invade the bronchial wall. (Author abstract) (9 Refs)

129. MUTAGENICITY AND TOXICITY OF FUROCOUMARINS: COMPARATIVE INVESTIGATIONS IN 2 TEST SYSTEMS.

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Mutat Res; 90(4):451-461 1981

Photomutagenicity and phototoxicity of the linear furocoumarins 8-methoxypsoralen (8-MOP) and 8-isoamylenoxypsoralen (8-IOP) and of the angular furocoumarin 5'-methylangelicin (5-MA) were studied. Human peripheral lymphocytes (HPL) were cultured in the presence of 5-bromodeoxyuridine. At 47 hr the cultures were exposed to 8-MOP (21.6 ug/ml), 8-IOP (27.0 ug/ml), or 5-MA (20.0 ug/ml). At 48 hr the cultures were irradiated with UV-A. Cells were examined at 72 hr. 8-MOP and UV or 5-MA and UV produced significant increases in the frequency of sister chromatid exchanges (SCE) compared with controls. 8-MOP had the greatest effect, increasing SCE by a factor of 2. 8-IOP had no effect. 5-MA produced irregular results. Cultures of an arginine-dependent strain of Chlamydomonas reinhardii were exposed to the test compounds and immediately irradiated with UV-A. Equimolar concentrations of 8-MOP and 5-MA produced equal levels of toxicity. 8-IOP produced much less toxicity in a longer time period. 8-MOP produced the greatest mutation rate, as indicated by induction of Arg+ revertants. 8-IOP produced similar mutation rates but required 3x the UV-irradiation time. 5-MA was much less mutagenic. Results indicate that monofunctional furocoumarins present a smaller mutagenic hazard than bifunctional furocoumarins and should be preferentially tested for therapeutic efficiency. (26 Refs)

130. MIXED-FUNCTION AMINE OXIDASE OF THE RAT HEPATOCYTE NUCLEAR ENVELOPE. DEMONSTRATION AND EFFECTS OF PHENOBARBITAL AND 3-METHYLCHOLANTHRENE.

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American Critical Care, 1600 Waukegan Road, McGaw Park, IL, 60085

Biochem Pharmacol; 31(1):69-73 1982

Mixed-function amine oxidase has been demonstrated in highly purified rat hepatocyte nuclear envelope. The enzyme was present in the nuclear envelope at a level 20% of that observed in microsomes. Induction studies indicated that nuclear envelope amine oxidase as well as its microsomal counterpart were refractory to the effects of phenobarbital and 3-methylcholanthrene. Phenobarbital administration increased the specific activity of the microsomal N,N-dimethylaniline N-demethylase and benzo[a]pyrene hydroxylase by 600 and 190%, respectively, but decreased the specific activity of the nuclear enzymes by 30-50%. In contrast, 3-methylcholanthrene increased the specific activity of benzo[a]pyrene hydroxylase in nuclear envelope and microsomes by 42-and 11-fold, respectively. The hydrocarbon also increased the microsomal and nuclear N,N-dimethylaniline N-demethylase by 40 and 60%, respectively, but the specific activity of microsomal and nuclear aniline 4-hydroxylase was decreased by 50%. Demonstration of amine oxidase in rat hepatocyte nuclear envelope implicates this enzyme in the toxicity and carcinogenicity of certain drugs and chemicals. (Author abstract) (71 Refs)

131. MUTAGENICITY OF DIPHENYLHYDANTOIN AND SOME OF ITS METABOLITES TOWARDS SALMONELLA TYPHIMURIUM STRAINS.

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Mutat Res; 103(3-6):219-228 1982

The mutagenicity of 5,5-diphenyl-hydantoin (DPH) and its major metabolite 5-(4-hydroxyphenyl)-5-phenylhydantoin (HPPH) were tested in vitro using S typhimurium strains TA 1535, TA 100, TA 1537, TA 1538, and TA 98. Neither DPH nor HPPH alone was mutagenic or cytotoxic at doses ranging from 1-1000 ug/plate. When mutagenicity was tested in the presence of liver S9 fraction from rats pretreated with different cytochrome P-450/448 inducers (corn oil; phenobarbital (PB)); beta-naphthoflavone; 3-methylcholanthrene 3-MC; Aroclor 1254, (PCB), DPH at concentrations of 25 ug/plate with 3-MC and 250 ug/plate with PCB pretreated rat S9 had limited mutagenic activity in strain TA 1538. Significant increases in revertant colonies were found with HPPH tested on strains TA98, TA1535, TA1537, and TA1538 when in the presence of S9 from BNF-, 3MC- and especially PCB-pretreated rats. These results are further supported by metabolic studies, which showed that HPPH and the other DPH metabolite 5-(3,4-dihydroxyphenyl)-5-phenylhydantoin (DHP) were formed when incubation of DPH was done in S9 fractions from livers of rats pretreated with BNF, 3MC or PCB, but not PB. Epoxide intermediates in the metabolism of DPH to HPPH and to HPPH to DHP may be responsible for the mutagenicity. A reaction mechanism is proposed. (21 Refs)

132. IDENTIFICATION OF THYMIDINE-5'-ALDEHYDE AT DNA STRAND BREAKS INDUCED BY NEOCARZINOSTATIN CHROMOPHORE.

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Proc Natl Acad Sci USA; 79(3):744-748 1982

Snake venom phosphodiesterase or endonuclease S1 digestion of neocarzinostatin chromophore-treated DNA, labeled in its thymidine residues, liberates an unusual labeled nucleoside from the 5' end of a drug-induced break. This substance, isolated by reverse-phase HPLC, possesses carbons from both the thymine and the deoxyribose moieties of thymidine in the DNA but, unlike thymidine, is readily degraded at pH 12 to thymine and a sugar fragment. The altered nucleoside was shown to contain a carbonyl group by its reduction with NaBH4 to form a substance that has the chromatographic properties of thymidine and by its reaction with various hydrazines to form the respective hydrazone derivatives; the carbonyl exists as the 5' aldehyde as shown by its mild chemical oxidation to the carboxylic acid with simultaneous loss of the 5' 3H. Mass spectral analysis showed a fragmentation pattern compatible with the structure thymidine-5'-aldehyde. These data indicate that the nonprotein chromophore of neocarzinostatin, in the presence of a reducing substance (2-mercaptoethanol) and molecular oxygen, selectively oxidizes the 5' carbon of nucleosides in DNA to the aldehyde, resulting in a strand break and a DNA fragment bearing nucleoside-5'-aldehyde at its 5' end. (Author abstract) (26 Refs)

133. STUDIES TO EVALUATE ARTIFICIAL SWEETENERS, ESPECIALLY REMSEN-FAHLBERG SACCHARIN, AND THEIR POSSIBLE IMPURITIES, FOR POTENTIAL MUTAGENICITY BY THE SALMONELLA/MAMMALIAN LIVER MICROSOME TEST.

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Mutat Res; 90(4):365-372 1981

Mutagenic activity (MA) of artificial sweeteners and some possible impurities of artificial sweeteners was studied in Salmonella typhimurium with or without metabolic activation by S9. S9 was prepared from livers of Sprague-Dawley rats. Bacterial cultures were exposed to saccharin (Sacc: less than or equal to 12,500 ug/plate), o-toluene sulfonamide or p-toluene sulfonamide (less than or equal to 18,000 ug/plate), o-sulfamoylbenzoic acid, p-sulfamoylbenzoic acid, o-sulfobenzoic acid, p-sulfobenzoic acid, phthalimide, anthranilic acid, disulfide salt, boiled saccharin, or one of three saccharin extracts (all less than or equal to 2,500 ug/plate), cyclamate (less than or equal to 12,500 ug/plate), or cyclohexylamine (less than or equal to 2,500 ug/plate). Cyclophosphamide (less than or equal to 100 ug/plate) and trypaflavine (less than or equal to 200 ug/plate) were used as positive controls. All Sacc tested was prepared by the Remsen-Fahlberg process. With the exception of one Sacc extract, all chemicals tested were negative for MA in the standard Ames assay. One organic extract of Sacc produced inconclusive results in three consecutive experiments. Results indicate that neither Sacc, cyclamate, cyclohexylamine, nor known impurities of the sweeteners are mutagenic in the Salmonella/mammalian liver microsome test. (23 Refs)

134. MUTAGENIC EFFECT OF AN ANTHRAQUINONE ON HUMAN LYMPHOCYTES.

Carballo MA, D'Aquino M, Aranda EI

Centro Nacional de Genetica Medica, Combate de los Pozos 2193, 1245 Buenos Aires, Argentina

Medicina (B Aires); 41(5):531-534 1981

The effect of 1,8-dihydroxyanthraquinone in dimethylsulfoxide on peripheral human lymphocytes was studied in vitro. A clastogenic effect was observed under the conditions employed. Synthetic and natural anthraquinones have wide distribution; they are used in food coloring, cosmetics, pharmaceuticals, and laxatives. (10 Refs) (In SPA)

135. LONG-TERM EFFECTS OF VINYL CHLORIDE ON EMBRYOGENESIS.

Sal'nikova LS, Vorontsov RS

Inst. Industrial Hygiene and Occupational Diseases, Moscow, USSR

Gig Tr Prof Zabol; (12):56 1981

Potential transplacental carcinogenic effect of vinyl chloride (VC) was studied in SHK mice. Pregnant females were subjected to inhalation exposure to VC at 35.3 and 4.8 mg/cubic meter. The offspring were followed up for 1-1.5 yr. The antenatal exposure to VC did not increase the incidence of malignant tumors. (6 Refs) (In RUS)

136. ELECTRON MICROSCOPIC OBSERVATIONS OF HEPATIC AND SUBCUTANEOUS HEMANGIOSARCOMAS INDUCED IN MICE EXPOSED TO VINYL CHLORIDE MONOMER.

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Am J Ind Med; 2(2):103-117 1981

Neoplastic effects of vinyl chloride were studied in mice in short exposure (4 wk) to low doses (1, 10, 100, 300, and 600 ppm). A mouse of the 10 ppm group developed a subcutaneous hemangiosarcoma, 29 wk after exposure. Histologically the tumor was localized in the subcutaneous connective tissue of the ear, and formed blood channels that appeared to be freely communicated. Neoplastic cells (NC) that directly lined the blood cavities were generally attenuated. Focal necrosis, hemorrhage, and hemosiderin deposition were observed. Ultrastructure of the attenuated NC was similar to that of capillary endothelium in the connective tissue. A mouse of the 600 ppm group developed an hepatic hemangiosarcoma approx 65 wk after exposure. The tumor was found on the surface of the lobe of the liver, and in addition, multiple pulmonary tumors were observed. The hepatic tumor showed formation of cystic blood channels, and the stroma of the tumor was frequently sclerotic. Neoplastic tissue contained degenerated hepatic parenchyma. NC lining the blood cavity were attenuated compared with normal sinusoidal endothelium. Pericyte-like cells were characterized by the presence of pinocytotic vesicles and dense bodies beneath the cell membrane. Under normal conditions the pericyte does not exist in Disse's space of the mouse. Alveologenic tumors were induced at high rate in mice 12 wk and longer after exposure; 23/24 mice in the 600 ppm group, 12/19 in the 300 ppm, 7/16 in the 100 ppm, 3/20 in the 10 ppm group, and in 2/38 control group. (28 Refs)

137. MUTAGENICITY AND TERATOGENICITY OF VINYL CHLORIDE MONOMER (VCM): EPIDEMIOLOGICAL EVIDENCE.

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Mutat Res; 98(1):97-100 1982

While there is little evidence to attribute isolated cases of hepatic angiosarcoma to to vinyl chloride monomer (VCM) exposure, it would be important if mutagenic or teratogenic effects of VCM could be demonstrated in the surroundings of factories or in the domestic environment of workers. In support of this thesis, a review of epidemiological studies was made to find supportive evidence in the form of excess infant deaths or birth defects. Although excess birth defects were found in an Ohio study, these could not be attributed to polyvinyl chloride (PVC) plants due to the nonuniform distribution within communities having plants and those without them up to 12 miles away. Although excess CNS-malformation in newborns was found in another study, in one of the towns with two PVC plants, none of the parents of involved patients worked at the plants. An attempt to determine infant death rates from pregnancies initiated before and after exposure of the same fathers to VCM or PVC fabrication have been confused by a number of factors. It was concluded that none of these studies were supportive of VCM or PVC plants being responsible for isolated hepatic angiosarcoma, excess infant death rates, or excess birth defects. (8 Refs)

138. A CARCINOGENIC BIOASSAY OF CERTAIN ROOFING MATERIALS.

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Am J Industr Med; 2(1):59-64 1981

A desire to determine the carcinogenic exposure of roofers from fossil fuel-derived sealers led to this study by the mouse skin test of coal tar pitch (CTP, traditional), coal tar bitumen (CTB, modern), roofing asphalt (RA), dust from stripping old CTP (CTPD), and benzo(a)pyrene (BaP, positive control). The CTPD was from a roof about 25 yr old. Fifty C3H/HeJ mice, weaning males quarantined for 2 wk prior to exposure, were used for each material, except 20 for CTPD. Twice a wk 50 mg of 1:1 (2/2) admixtures with toluene (negative control) was applied to the back (reclipped biweekly) for 80 wk or until diagnosis of papilloma development. The papilloma was allowed to progress to carcinoma before sacrifice and histopathologic confirmation. Using average time of appearance of first papilloma, carcinogenic activity was graded thusly (time in wk, BaP content in percentage): CTPD (16.5, 0.08), CTP (18.0, 0.064), CTB (20.5 and 0.064, 21.5 and 0.072), BaP (31.8, 0.1), RA (greater than 80, less than 0.0004). At the 95% confidence level, CTPD, CTP, and CTB were judged significantly more carcinogenic than BaP, and CTPD and CTP more so than CTB. CTPD and CTP were judged statistically equal. Reduction of exposure to CTPD was urgently recommended, especially in view of its adherent quality. Reliance only on BaP content was considered insufficient. (10 Refs)

139. HYDROCARBON-BASED OILS AS INDUCERS OF CUTANEOUS ARYL HYDROCARBON HYDROXYLASE.

Rahimtula AD, Payne JF, Martins I
Dept. Biochemistry, Memorial Univ. Newfoundland, St. John's, Newfoundland, A1B 3X9, Canada
Toxicol Lett; 10(2):213-217 1982

Modulation of drug-metabolizing mixed-function oxidase activity in the skin of rats by various petroleum mixtures was investigated. Skin application of Aroclor 1254 caused a 10-fold induction of benzo(a)pyrene (BAP) 3-hydroxylase activity and a 6 fold increase in diphenyloxazole (PPO) hydroxylase activity. Kuwait crude, used crankcase oil, and Fuel Oil NO. 2 applied to the skin also induced B AP hydroxylase and PPO hydroxylase to a lesser degree. Ip administration of Kuwait crude and used crank-case oil induced both hepatic BAP 3-hydroxylase and PPO hydroxylase activity. Cytochrome P 450 might play a significant role in the biotransformation of various chemicals and dermatologic medications. (9 Refs)

REVIEWS AND OTHER COMPOUNDS

140. LOSS OF FIBRONECTIN AMONG THE SELECTIVE SURFACE PROTEIN CHANGES ASSOCIATED WITH P-FORMALDEHYDE PROMOTED MEMBRANE VESICULATION.

Rieber M, Rieber MS
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Biochem Biophys Res Commun; 104(2):844-850 1981

Radioiodination followed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis was used to detect proteins in vesicle fractions released when cultured cells were subjected to 25 milli(m)M p-formaldehyde and 2 mM dithiothreitol (DTT). Surface iodination of 'normal' WIRL-3 cells, 'transformed' R72/3 cells, normal rat kidney fibroblasts, and Rat-1 normal fibroblasts revealed upon electrophoresis a major 220 kilodalton (kd) fibronectin-like component. Vesiculation induced by the p-formaldehyde/DTT treatment decreased the component in all but the Rat-1 cells, and increased the lower mol wt fibronectin components, whether iodination took place before or after chemical vesiculation induction. In Rat-1 cells the vesiculation treatment caused a decrease in a surface-associated 140 kd component with an increase in a 130 kd component in the vesicular fraction. The release and selective degradation of cell surface proteins upon chemical vesiculation may involve surface protease activation. (12 Refs)

141. CYTOGENETIC EFFECTS ON THE EASTERN MUDMINNOW, UMBRA PYGMAEA, EXPOSED TO ETHYL METHANESULFONATE, BENZO[A]PYRENE, AND RIVER WATER.

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Ecotoxicol Environ Saf; 5(3):261-269 1981

The eastern minnow, Umbra pygmaea, was exposed to two known genotoxic agents and to water from the Rhine river at Lobith, The Netherlands. Both chromosome aberrations and sister chromatid exchanges (SCE) were scored. Fish were exposed to 0, 8, 40, and 200 mg ethylmethanesulfonate (EMS)/liter and 0, 10(-5), and 10(-4) mg benzo[a]pyrene (BaP)/liter at 20 C for 48 hr. Two additional groups of fish were exposed to 10(-4) mg/liter BaP for 4 and 6 days. EMS induced chromatid breaks, chromosome breaks, and gaps in gill and fin tissue; most of the aberrations were chromatid aberrations. EMS concentrations of 8, 40, and 200 mg/liter induced 1.1, 6.8, and 19.6% metaphases with aberrations, respectively. BaP only induced chromosome aberrations in fish exposed to the higher concentration; both chromatid breaks and gaps were seen. Activity of benzo[a]pyrene hydroxylase was near the detection limit (0.01 umole/g liver/h r). Bromodeoxyuridine injection to improve the number of metaphases with differential staining gave best results in gill tissue after two or three injections. Rhine water induced chromosome aberrations (chromatid breaks, chromosome breaks, gaps) and increased the number of SCE/metaphase. U pygmaea was suitable for detecting cytogenetic effects of chemical pollution in the aquatic environment. (18 Refs)

142. THE DISTRIBUTION OF INDUCED SISTER-CHROMATID EXCHANGES: A TOOL FOR IDENTIFYING AGENTS DIRECTLY INTERACTING WITH DNA.

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Mutat Res; 103(3-6):333-337 1982

Exponentially-growing V79-AP4 Chinese hamster cells were treated for 1 hr with the direct alkylating agent ethyl methanesulfonate (EMS: 1) and 10 milliM and the DNA-synthesis inhibitors 5-bromodeoxyuridine (BUdR: 0.4, 0.8, 1.6 milliM) and aphidicholine (APC: 5, 10, 20 ug/ml). THe frequency distributions of sister-chromatid exchanges (SCEs) were not changed after EMS, although the mean number of SCEs increased with concentration. With BUdR and APC the median SCE/cell was about the same for all concentrations, but the spread of the frequency distribution was markedly increased as concentrations of both agents increased. Comparing SCE distribution patterns in this manner makes it possible to determine whether SCEs were induced by factors inside DNA (damaged template, EMS) or outside DNA (damaged replication machinery, BUdR, APC). (11 Refs)

143. ONTOGENETIC VARIATION IN RAT LIVER, LUNG AND KIDNEY MONOOXYGENASE INDUCTION BY LOW DOSES OF BENZO(A)PYRENE AND CIGARETTE-SMOKE CONDENSATE.

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(c/o Gielen) Laboratoire de Chimie Medicale, Institut de Pathologie, Universite de Liege, Batiment B 23, Belgium
Br J Cancer; 44(6):902-910 1981

The specific lung-AHH induction, which we previously observed after the inhalation of cigarette smoke, is not due to the route followed by the inhaled smoke, for the same phenomenon occurs after ip injection of either cigarette smoke condensate (CSC) or benzo(a)pyrene in low doses. In this respect lung AHH behaves completely differently from the liver and kidney enzyme, in which organs, basal AHH activity (which is low in the fetus) increases rapidly after birth to reach the adult level 2 mo later, and is only inducible by CSC and low doses of BP in unweaned rats. In the lung, the basal AHH activity (low in the fetus) increases abruptly at birth, peaks in 5-day-old rats and then decreases slightly. Contrary to enzyme activity in other tissues, lung AHH cannot be induced in unweaned young animals. The enzyme subsequently becomes sensitive to inducing agents and is highly inducible in 90-day-old rats. Similar behavior occurs in two other enzymes linked to cytochrome P1450:

ethoxycoumarin deethylase and ethoxyresorufin deethylase. The results could be related to the particular susceptibility of the lung to develop cancer after the inhalation of cigarette smoke. (Author abstract) (38 Refs)

144. HOST-MEDIATED MUTAGENESIS FOR DETECTION OF MUTAGENS/CARCINOGENS.

Inui N, Nishi Y
Section Cell Biology and Cytogenetics, Biological Res. Center, Japan Tobacco and Salt Public Corporation, Nakogi 23, Hatano, Kanagawa 257, Japan
Gann Monogr Cancer Res; 27:73-84 1982

An in vivo-in vitro combination assay, host-mediated transplacental mutation assay (HTMA), has been established in which somatic cell mutations can be detected and measured quantitatively. Two genetic markers, 8-azaguanine resistance (8AGr) and 6-thioguanine resistance, were used for detection of forward mutations in fibroblasts of Syrian hamster embryos in pregnant mothers. Mutation frequencies increased linearly with increases in the dose of furylfuramide up to 100 mg/kg body wt of the mothers, when given ip or po; higher mutagenicity was observed following po administration than after ip treatment. Data obtained by HTMA on the effects of coadministration of secondary amines and nitrite, which result in formation of nitrosamines, are presented. Administration of morpholine plus sodium nitrite (500 mg/kg, each) markedly enhanced the mutagenic effect. Coadministration of aminopyrine and sodium nitrite had a more mutagenic effect on hamster embryonic cells than single administration of either compound alone. Thus, N-nitroso compounds produced in the body do cause gene mutations in embryonic tissues and organs. The induction of 8AGr mutations was studied in cultured cells from various organs of embryos of pregnant hamsters treated with benzopyrene (BP), nitrosodimethylamine (DMN), and N-nitrosoethylurea (NMU). Treatment with BP at 200 mg/kg produced more 8AGr mutations in embryonic lung cells than in kidney, liver, or brain cells. DMN (200 mg/kg) produced the highest frequency of 8AGr mutations in the embryo liver cells. After NME administration, there was marked increase in 8AGr mutations in brain cells. Detection of somatic mutations by HMTA is discussed. (45 Refs)

145. AN EVALUATION OF TESTS USING DNA REPAIR-DEFICIENT BACTERIA FOR PREDICTING GENOTOXICITY AND CARCINOGENICITY. A REPORT OF THE U. S. EPA'S GENE-TOX PROGRAM.

Leifer Z, Kada T, Mandel M, Zeiger E, Stafford R, Rosenkranz HS
Dept. Microbiology, New York Medical Coll., Valhalla, NY, 10595
Mutat Res; 87(3):211-297 1981

Methods for detection of DNA-damaging agents by repair-deficient bacterial assays are reviewed and recommendations for their improved use are made. Literature through April 1979 was searched and 91/276 papers contained analyses of 611 compounds that had been assayed in one or more of 55 pairs of repair-proficient and repair-deficient strains (38 Escherichia coli, 11 Bacillus subtilis, and 6 Proteus mirabilis). Test results and carcinogenicity data were compared in polA and other E coli, and E coli polA and B subtilis systems. In the E coli polA system, 100/269 compounds tested were positive, 35 negative and 134 gave No Test (NT) by the spot method; 24 of the latter compounds tested were also positive in the liquid assay technique. Among 45 compounds with a NT result, 23 were positive in the liquid assay and 22 were negative. When the E coli polA system was compared with other E coli strains, agreement of results was observed for 10 compounds, while 7 that were positive with polA and some of the other E coli strains were negative with WP2uvrA. A 78% correspondence between E coli polA and B subtilis rec assays was observed. Of 71 carcinogens assayed by the polA system, 44 were positive, 10 negative, and 17 gave NT or doubtful results. Of 56 carcinogens assayed with B subtilis, 21 were positive, 9 negative and 26 were NT or doubtful. One noncarcinogen tested in each assay was positive. Of the seven carcinogens assayed in P mirabilis, six were positive. E coli detected the highest percentage of alkyl epoxides and hydroxylamines; B subtilis rec the highest percentage of nitrosamines and sulfur and nitrogen oxides. Advantages and disadvantages of DNA repair assays in bacteria are listed. (98 Refs)

146. MUTAGENIC EVALUATION OF CARCINOGENS AND NON-CARCINOGENS IN THE L5178Y/TK ASSAY UTILIZING POSTMITOCHONDRIAL FRACTIONS (S9) FROM NORMAL RAT LIVER.

Amacher DE, Turner GN
Drug Safety Evaluation Dept., Pfizer Central Res., Groton, CN, 06340
Mutat Res; 97(1):49-65 1982

The detection capabilities of the modified mouse lymphoma L5178Y TK+/- to TK-/- mutation assay were tested using 5% (vol/vol) S9 from rodents (usually Sprague-Dawley rat) which had not been treated with enzyme inducers. Most suspected carcinogens (7/10) caused a doubling of mutant frequency compared to solvent controls in a minimum of one experiment, at treatment levels permitting at least 61% cell survival; the exception was 4-nitrobiphenyl, which was considered mutagenic when two-sample loge t-test was done. Thioacetamide, a carcinogen, was negative for both the 5% noninduced S9 and the 10% Aroclor 1254-induced S9 tests. Dimethylcarbamyl chloride and glycidaldehyde were mutagenic in the absence of S9 but showed diminished activity in the presence of 10% S9. Styrene oxide was also mutagenic without S9. Noncarcinogens (6/8) were negative for mutagenicity in the present test; exceptions were chloracetic acid and p-aminophenol. (18 Refs)

147. COMPARATIVE EVALUATION OF DIFFERENT PAIRS OF DNA REPAIR-DEFICIENT AND DNA REPAIR-PROFICIENT BACTERIAL TESTER STRAINS FOR RAPID DETECTION OF CHEMICAL MUTAGENS AND CARCINOGENS.

Suter W, Jaeger I
Preclinical Res. Dept. Toxicology Unit, Sandoz Ltd., Basle, Switzerland
Mutat Res; 97(1):1-18 1982

Carcinogenic and noncarcinogenic compounds, including antibiotics, polycyclic aromatics, aromatic amines, alkyl halides, esters, epoxide carbamates and related compounds, nitroaromatics and heterocyclics, nitroso compounds, hydrazine compounds, azo compounds, and other bioactive agents, were tested for mutagenicity with the agar incorporation test (AT) and the spot test (ST). Two paired (DNA repair proficient/repair deficient) Bacillus subtilis systems, H17/M45 and HLL3g/HJ-15, were used, and the repair-proficient Escherichia coli A1157 strain was paired with the repair-deficient strains JC2921, JC2926, JC5519, and JC5547. Results were compared with reported carcinogenicity and/or Ames test mutagenicity, or in some cases with Ames Salmonella (TA1535, TA1537, TA1538, TA98, TA100) assays reported here for the first time. E coli systems yielded a high number of 'no result' findings as well as many false-positive outcomes. B subtilis systems were generally reliable indicators of carcinogenicity, especially if both AT and ST were used. The bacterial DNA-repair tests agreed more often with the Ames test than with carcinogenicity results. When both pairs of B subtilis strains were combined with the Ames assay, excess false-positives did not appear, whereas the number of false-negative findings with carcinogens was reduced. The slightly increased probability of uncovering a suspected carcinogen does not seem to justify inclusion of the extra tests in a battery, except when working with chemicals of classes in which the Ames test is known to be less sensitive. (59 Refs)

148. ASPERGILLUS NIDULANS: SYSTEMS AND RESULTS OF TESTS FOR CHEMICAL INDUCTION OF MITOTIC SEGREGATION AND MUTATION. I. DIPLOID AND DUPLICATION ASSAY SYSTEMS. A REPORT OF THE U. S. EPA GENE-TOX PROGRAM.

Kafer E, Scott BR, Dorn GL, Stafford R
Dept. Biology, McGill Univ., 1205 Ave. Docteur Penfield, Montreal H3A 1B1, Canada
Mutat Res; 98(1):1-48 1982

A critical summary of the 1965-1978 literature is made and background information on the test fungus is presented which covered a wider time period. Most of the reported test systems measured frequency of homo- or hemizygous segregants in heterozygous diploids. These could detect non-mutation genetic damage effects on spindles as well as a variety of types of mutations. However, the different procedures involved made for noncomparable results with the same chemical. Another test system measured increases in frequency of recessive lethals, or effects on recovery of haploid second-order segregants; it was similar to known tests in Drosophila. A third system measured effects on frequency of haploid sectors from duplication strains; it was limited by the availability of a single useful duplication strain. Results on 71 chemicals, including some antineoplastic agents and fungicides, were tabulated. Results of the more elaborate test systems pointed towards the appropriate mammalian system for higher level evaluation. More chemicals need to be tested to fully evaluate the utility of these three basic systems, and more experimental detail is needed on others. Emphasis was put on future use of positive and/or negative controls, full disclosure of results and procedures, use of more than one dose and/or adequate sample size, and proper statistical treatment. (97 Refs)

149. THE MODIFYING EFFECT OF HEXAVALENT CHROMATE ON THE MUTAGENIC ACTIVITY OF THIO-TEPA.

Paschin YV, Kozachenko VI
Lab. Environmental Mutagens, Inst. General Genetics Acad. Sciences, Moscow 117809, USSR
Mutat Res; 103(3-6):367-370 1982

Logarithmically-growing cultures of Chinese hamster V79 cells were exposed to different concentrations of potassium dichromate (PD) or triethylene thiophosphoramide (thio-TEPA) for 2 hr, washed, in sterile Hank's soln, and incubated for 96 hr before 8-azaguanine selection and plating. The mutagenic effects of PD (0.5 ug/ml) and thio-TEPA (2 ug/ml) were virtuallly identical mutant frequencies: (11.2 vs 11.4, x 10(-5)), with little effect on the viability of cells. The same compounds together yielded a mutation frequency of 9.6 x 10(-5), but plating efficiency was reduced form 86% (PD) or 95% (thio-TEPA) to 67%. Administration of PD for 2 hr followed by thio-TEPA for 2 hr resulted in a mutation frequency of 20.7 x 10(-5), and a plating efficiency of only 12%. Thio-TEPA seems to act as a protectant in the combined administration by reducing hexavalent CR to the trivalent, nonmutagenic form; serial administration of the two mutagens results in an additive effect. (6 Refs)

150. EVALUATION OF RELATIVE ENVIRONMENTAL HAZARDS FROM A COAL GASIFIER.

Gangwal SK, Cleland JG, Truesdale RS
Research Triangle Inst., Research Triangle Park, NC
Evaluation of Relative Environmental Hazards from a Coal Gasifier. Available from National Technical Information Service, Springfield, VA, as PB81-217648:, 108 pp., 1981.

The report gives results of an evaluation of relative environmental hazards from a laboratory-scale coal gasifier. Detailed chemical analyses of four effluent streams (gas, aqueous condensate, tar, and ash) were performed for more than 30 gasification runs on a variety of coals, from lignite to bituminous. It briefly describes the gasification reactor, the associated sampling and analysis system, problems encountered with analyses, and special techniques for analyzing complex samples. Relative environmental hazards were determined using the Multimedia Environmental Goals methodology. Toxicity and mutagenicity were assessed using bioassay data. More than 400 effluent stream constituents were identified. Environmentally, the most significant effluent stream is aqueous condensate, followed by tar, product gas, and ash. However, on an equivalent weight basis, the tar stream is more toxic and mutagenic than aqueous condensate. Polycyclic aromatic hydrocarbons and organic bases are the most mutagenic fractions of the tar. Coal pyrolysis and gasification at higher temperatures leads to reduced tar mutagenicity. The most environmentally significant constituents (by stream) are: (1) product gas-CO, benzene, H2S, and carbonyl sulfide; (2) aqueous condensate - phenol/cresols/xylenols (PCX), NH3, sulfides, thiocyanates, CN, As, and chlorides; and (3) ash - As, Ni, Be and Se. (Author abstract)

151. EFFECTS OF LONG-TERM EXPOSURE TO LOW LEVELS OF OZONE: A REVIEW.

Melton CE
Civil Aeromedical Inst., Federal Aviation Admin., Oklahoma City, OK, 73125
Aviat Space Environ Med; 53(2):105-111 1982

Reports on long-term effects of ozone in animals and humans are reviewed. Ozone concentration is apparently more important than duration of exposure in determining effects. Only three references to tumorigenicity were noted: one study found ozone to be a pulmonary carcinogen after exposure of tumor-resistant mice to 2.5 ppm (vol/vol) 2 hr/day for 120 days, another showed a macrophage-ozone concentration relationship in dogs exposed to 2-3 ppm (vol/vol) 8 hr/day for 18 mo, and a third report attributed pulmonary adenomas in lung tumor-susceptible mice to chronic exposure to damaging levels of ozone. (39 Refs)

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1. AN EVALUATION OF THE GENETIC TOXICITY OF EPICHLORHYDRIN. A REPORT OF AN EXPERT GROUP OF THE INTERNATIONAL COMMISSION FOR PROTECTION AGAINST ENVIRONMENTAL MUTAGENS AND CARCINOGENS.
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(c/o Rajewsky) Institut fur Zellbiologie (Tumorforschung), Universitat Essen (GH), Hufelandstrasse 55, Essen 1, W. Germany
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Scalabrino G, Ferioli ME
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AUGUST, 1982

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HYDRAZINES AND RELATED COMPOUNDS

1. EFFECT OF AGING ON THE DEVELOPMENT OF 1,2-DIMETHYLHYDRAZINE-INDUCED INTESTINAL TUMORS IN MICE.

Turusov VS, Lanko NS, Parfenov IuD
Lab. Carcinogenic Agents, All-Union Cancer Res. Center, Moscow, USSR
Biull Eksp Biol Med; 91(12):705-707 1981

Relationship between carcinogenesis and aging was studied in young (2 mo old), mature (8 mo old), and old (12 mo old) female CBA mice. Animals received sc injections of 1,2-di-

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methylhydrazine (DMH: 8 mg/kg, 1x/wk). Animals were followed up for 26-35 wk after the initiation of DMH administration, and the incidence of tumors of the large intestine was determined. An overall incidence of tumors in young, mature, and old mice was 13.1%, 61.0%, and 69.1%, respectively. The frequency of infiltrating tumors was 6%, 30.5%, nad 54.3%, respectively. Analysis of time-effect curves showed that the median latent period of tumor development in young mice was approx 1.8x greater than that in old mice and 1.4x greater than that in mature mice. The differences in the chemical carcinogenesis were explained by elevated activity of beta-glucuronidase in the large intestine of old mice. (7 Refs) (In RUS)

2. EFFECTS OF DELAYS IN THE CELL CYCLE ON THE INDUCTION OF PRENEOPLASTIC AND NEOPLASTIC LESIONS IN RAT LIVER BY 1,2-DIMETHYLHYDRAZINE.

Ying TS, Enomoto K, Sarma DS, Farber E
Dept. Pathology, Univ. Toronto, Toronto, Ontario M5G 1L5, Canada
Cancer Res; 42(3):876-880 1982

This study was designed to explore further the relationship between cell proliferation and the induction of early putative preneoplastic lesions by carcinogens. Rats were given a nonnecrogenic dose of 1,2-dimethylhydrazine 24 hr before being subjected to partial hepatectomy. Beginning 4 hr later, hydrocortisone was injected 10x at 4-hr intervals to delay progression through the cell cycle, including inhibition of DNA synthesis by at least 85% for about 40 hr. At the appropriate time thereafter, the putative preneoplastic hepatocytes were selectively stimulated to grow in vivo into gamma-glutamyltransferase-positive focal lesions. Animals given hydrocortisone showed a large decrease (71%) in the number of gamma-glutamyltransferase-positive foci. In contrast, when hydrocortisone was given at 6 days after partial hepatectomy, no inhibition in the induction of hepatic lesions was observed. In the next experiments, rats were treated with 1,2-dimethylhydrazine and were subjected to partial hepatectomy at 12, 24, or 84 hr or 1 wk thereafter. A significant number of gamma-glutamyltransferase-positive foci was found when partial hepatectomy was performed at 12 or 24 hr but far fewer were found when the operative partial hepatectomy was delayed to 48 hr or 1 wk later. Similarly, in long-term experiments, 6 of 14 animals developed primary hepatocellular carcinoma 13 mo after the time of injection of 1,2-dimethylhydrazine when partial hepatectomy was performed at 12 hr, while none of the animals developed liver cancer when the operation was performed at 48 hr. These results imply that the majority of biochemical lesions induced by 1,2-dimethylhydrazine that are relevant to the induction of liver preneoplasia and neoplasia are short-lived and that their persistence is associated with some cellular activity closely related to the cell cycle. (Author abstract) (39 Refs)

3. 1,2-DIALLYLHYDRAZINE DIHYDROCHLORIDE CARCINOGENESIS IN MICE.

Toth B, Nagel D
Eppley Inst. Res. in Cancer and Allied Diseases, Univ. Nebraska Medical Center, Omaha, NE, 68105
Oncology; 39(2):104-108 1982

Continuous administration of 0.0625% 1,2-diallylhydrazine dihydrochloride in drinking water for life to 6-week-old randomly bred to Swiss mice induced lung tumors. In comparison with the untreated controls, the lung tumor incidence rose from 25 to 80% in the females and from 26 to 80% in the males. The treatment had no apparent effect on the development of other tumor types. Histopathologically, the lesions were classified as adenomas and adenocarcinomas of the lungs. The work is a continuation of our structure activity inquiry concerning the relative carcinogenic potencies of the dialkyl versus the monoalkyl series of hydrazine analogues. (Author abstract) (28 Refs)

4. REGION-SPECIFIC PATTERNS OF MUCIN REACTION DEMONSTRATED BY PARADOXICAL CONCANAVALIN A-STAINING IN NORMAL COLONIC EPITHELIUM AND IN COLORECTAL CANCERS INDUCED IN RATS BY 1,2-DIMETHYLHYDRAZINE.

Tatematsu M, Katsuyama T, Nakanowatari J, Hasegawa R, Imaida K, Fukushima S, Ito N
First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
Gan; 73(1):77-84 1982

The histochemistry of mucin in normal large intestine and in experimental colorectal cancers induced in Wistar rats with 1,2-dimethylhydrazine was analyzed by modifications of the concanavalin A-horseradish peroxidase method (paradoxical concanavalin A-staining) and high-iron diamine-Alcian blue (pH 2.5) staining (HID-AB). Quantitative analysis of each mucin reaction was done by the use of an image analyzer. Regional variations in the percentage area of 'labile class III mucin' were 1 to 50% in the distal colon and 50 to 90% in the proximal colon. Regional variations in the percentage area of sulfated sialomucin were 80 to approx 100% in the distal colon and under 20% in the proximal colon. The percentage area of 'labile class III mucin' in primary colorectal cancers showed region-specific variation and that in metastatic colorectal cancers also showed similar region-specific variation of colorectal mucosa where primary tumors were located. In contrast, there were no region-specific mucin reactions for sulfated sialomucin in almost all primary and metastatic colorectal cancers. (Author abstract) (17 Refs)

HETEROCYCLIC COMPOUNDS

5. A REDUCED CAPACITY FOR UNSCHEDULED DNA SYNTHESIS IN LYMPHOCYTES FROM INDIVIDUALS EXPOSED TO PROPYLENE OXIDE AND ETHYLENE OXIDE.

Pero RW, Bryngelsson T, Widegren B, Hogstedt B, Welinder H
Wallenberg Lab., Biochemical and Genetic Ecotoxicology, Univ. Lund, Box 7031, S-220 07 Lund 7, Sweden
Mutat Res; 104(1-3):193-200 1982

Inhibition of unscheduled DNA synthesis (UDS) was studied in 23 workers (25-59 yr old, mean age 41 yr) exposed to propylene oxide (PO) as process workers for 1-20 yr (mean 10 yr) and in 5 male workers (25-44 yr old, mean age 32 yr) exposed to ethylene oxide (EO) as sterilizing, packing, or truck-driving personnel for 0.3-5 yr (mean 2.9 yr). Eighteen of 23 PO-exposed workers were smokers. Controls were 12 male workers (21-46 yr old, mean age 30 yr) not exposed occupationally to any mutagenic chemical compound. Five of the controls were smokers. UDS induced by N-acetoxy-2-acetylaminofluorene (NA-AAF) and NA-AAF binding to DNA were the methods used. Use of [3H]NA-AAF enabled the direct assessment of initial NA-AAF damage to DNA, which in turn served as the substrate for induction of UDS, and thereby repair of NA-AAF lesions in the DNA. Lymphocyte samples from both the controls and the PO-exposed workers varied considerably in values for NA-AAF-induced UDS. UDS variation was dependent on the level of NA-AAF bound to DNA after a 30-min incubation of lymphocytes in the presence of 10 uM [3H]NA-AAF. The correlation coefficients between NA-AAF-induced UDS and NA-AAF binding to DNA were highly significant for both the controls and PO-exposed workers. PO-plus EO-exposed workers exhibited significant reductions in NA-AAF-induced UDS when compared to the controls. The level of [3H]NA-AAF covalent binding to DNA was not significantly reduced by PO- and EO-exposure. Results indicate that exposure to relatively low doses of PO and EO can cause individuals to be at increased risk due to a reduced capacity to repair DNA lesions. (12 Refs)

6. THE MUTAGENIC EFFECTS OF DIEPOXYBUTANE IN WILD-TYPE AND MUTAGEN-SENSITIVE MUTANTS OF DROSOPHILA MELANOGASTER.

Olsen OA, Green MM
Inst. General Genetics, Univ. Oslo, P.O. Box 1031 Blindern, Oslo 3, Norway
Mutat Res; 92(1/2):107-115 1982

The effects of 1,2,3,4-diepoxybutane (DEB) on two X-chromosome loci (w and y) of Drosophila were studied. At least one-third of the DEB-induced mutations were chromosome deletions. The nature of the DEB-induced complementary mutants was not clear. Some of the mutants were mosaics, expressed somatically but not transmitted in the germ line. Somatic sensitivity to DEB was demonstrated by 9/11 methyl methanesulfonate (MMS)-sensitive mutants. The MMS-sensitive and DEB-insensitive mutants were also somatically insensitive to nitrogen mustard and UV (one was also insensitive to x-rays), suggesting that these mutants (mus103 and mus105) may not be involved in DNA replication or repair. In direct genetic experiments, females homozygous for at least 2/6 and probably 5/6 MMS-sensitive mutants showed an impaired capacity to repair DEB-induced damage in spermatozoa. Females homozygous for MMS-sensitive mutant mus201 showed an unimpaired capacity to repair DEB-induced genetic damage. (15 Refs)

7. NOTE ON THE UTILITY OF THE ST MUS302 TEST FOR CHROMOSOME LOSS IN A BLIND TEST OF AN ENVIRONMENTAL COMPOUND FOR CHROMOSOME BREAKAGE IN DROSOPHILA.

Zimmering S
Div. Biology and Medicine, Brown Univ., Providence, RI, 02912
Mutat Res; 104(1-3):117-119 1982

A compound identified as beta-propiolactone (BP) was tested for chromosome breakage in the heritable translocation test, using Drosophila females from the repair-deficient strain st mus302. Results of sex-linked lethal tests for point mutations and heritable translocation tests to detect translocations between chromosomes 2 and 3 and between the Y chromosome and chromosome 2 and/or 3 were positive. Xc2, y f/BSYy+ males were treated with 7.5 mg/ml BP and mated as follows: in Experiment I, to mei-9a and st mus 302 females and in Experiment II, to repair-proficient and st mus302 females. With mei-9a females, significant increases in both complete and partial chromosome loss were observed; the frequency of total loss was 2.2%, greater than the induced translocation cited for other tests. With st mus/302, a substantially stronger effect was found, the total loss reaching 13.8%. In Experiment II, results with repair-proficient females failed to indicate a significant increase in chromosome loss, whereas with st mus302 total loss was 10.1%. (7 Refs)

8. METABOLISM AND ACTIVATION OF AFLATOXIN B1 BY RECONSTITUTED CYTOCHROME P-450 SYSTEM OF RAT LIVER.

Yoshizawa H, Uchimaru R, Kamataki T, Kato R, Ueno Y
(c/o Ueno) Dept. Toxicology and Microbial Chemistry, Science Univ. Tokyo, Ichigaya, Shinjuku-ku, Tokyo 162, Japan
Cancer Res; 42(3):1120-1124 1982

Metabolism and activation of aflatoxin B1, a potent hepatocarcinogenic and mutagenic mycotoxin of Aspergillus flavus, were investigated in the reconstituted enzyme system composed of purified NADPH-cytochrome P-450 reductase and cytochrome P-450 or P-448 or rat liver. The aflatoxin M1 formation was strictly mediated by P-448 purified from the liver microsomes of polychlorobiphenyl- and 3-methylcholanthrene-treated rats, while the aflatoxin Q1 formation, as well as the binding to DNA, were catalyzed by both P-450 and P-448. Differences between the kinetic data on metabolism and activation of aflatoxin B1 obtained with the reconstituted cytochrome systems and those obtained with the microsomal and nuclear systems were discussed, and the significance of these biochemical data in the in vivo carcinogenicity of aflatoxin B1 was evaluated. (Author abstract) (37 Refs)

9. THE CHEMICAL ACTIVATION OF NON-MUTAGENIC NITRATED POLYCYCLIC AROMATIC HYDROCARBONS TO MUTAGENS.

Karpinsky GE, McCoy EC, Rosenkranz HS
Center for the Environmental Health Sciences, Case Western Reserve Univ. Sch. Medicine, Cleveland, OH, 44106
Mutat Res; 92(1/2):29-37 1982

Ames assays in Salmonella strains TA1535, TA100, TA98, and nitroreductase (NRase)-deficient strains TA100NR and TA98NR were performed with 5-nitroquinoline (5-NQ), 6-nitroquinoline (6-NQ), 8-nitroquinoline (8-NQ), 1,8-dinitronaphthalene (1,8-DNN), 1,5-dinitronaphthalene, 4-nitroquinoline 1-oxide, 2-nitrofluorene, and nitrofurantoin, in the presence or absence of rat liver microsomes (S9 mix). Both 5-NQ and 6-NQ were direct-acting bacterial mutagens, but 8-NQ (a carcinogen in rats) and 1,8-DNN (an analog of 8-NQ) were not mutagenic even in the presence of S9 mix. The non-mutagenicity of 8-NQ and 1,8-DNN could be overcome chemically, in situ, by the addition of zinc (Zn) dust. Anaerobic conditions were not required for a max yield of the mutagenic product of 1,8-DNN. The mutagenicity of the 1,8-DNN product was not due to a nitro function, as shown by the fact that it was fully active even in the NRase-deficient strain TA100NR. It is concluded that although bacteria can reduce some nitrated polycyclic aromatic hydrocarbons (N-PAH) to mutagens, their NRases cannot reduce the nitro functions of all N-PAHs to the proximate mutagenic hydroxylamines. Chemical reduction of the N-PAH (ie, non-enzymatic activation) with Zn (which is compatible with the Ames bioassay) may be a useful addition to the procedure in the evaluation of the potential mutagenicity of nitro-containing chemicals. (24 Refs)

10. GENETIC TOXICOLOGY STUDIES WITH 2-NITROBENZOFURANS AND 2-NITRONAPHTHOFURANS.

Weill-Thevenet N, Buisson JP, Royer R, Hofnung M
Unite de programmation moleculaire et toxicologie genetique, CNRS, L.A. 271, INSERM U 163, Institut Pasteur, 28 rue du Docteur Roux, 75015 Paris, France
Mutat Res; 104(1-3):1-8 1982

The mutagenic activity of three 2-nitronaphtho[2,1-b]furans, two 2-nitronaphtho[3,2-b]furans, and two 2-nitronaphtho[1,2-b]furans was tested using the Salmonella/microsome assay (Mutatest). The seven compounds gave a mutagenic response with the following characteristics: it occurs on strains TA1537, TA1538, TA98, and TA100, but not no strain TA1535; the mutagenic response is partially dependent on the bacterial nitroreductase activity and is lower in the presence of an activating mixture S9 from rat liver; it varies quantitatively and qualitatively with the structure of the compound. The mutagenic responses of the 2-nitronaphthofurans and three 2-nitrobenzofurans was also examined in a phage-induction assay (Inductest). The mutagenic potency measured in the Mutatest correlated well with that measured by the Inductest; those compounds which were negative in the Mutatest were also negative in the Inductest. The mutagenic activity of the two most potent mutagens examined was tested using strains TA1978 and TA2421, the UVr+ counterparts of the TA1538 and TA98 uvrB excision-repair mutants used in the Mutatest. The mutag enic response was reduced by at least a factor of 100 compared to the uvrB mutants, indicating that the excision-repair system is efficient in preventing the mutagenic effect of the 2-nitronaphthofurans. 2-Nitro-7-methoxynaphtho[2,1-b]furan (R7000), one of the most potent compounds, also induced sperm abnormality in mice (Spermatest). The results of the bacterial tests and Spermatest in relation to the possible genetic toxicity of these compounds is discussed. (11 Refs)

11. THE MUTAGENIC POTENCY OF 1,8-DINITROPYRENE IN CULTURED MOUSE LYMPHOMA CELLS.

Cole J, Arlett CF, Lowe J, Bridges BA
MRC Cell Mutation Unit, Univ. Sussex, Falmer, Brighton, Sussex BN1 9QG, England
Mutat Res; 93(1):213-220 1982

The mutagenic potency of 1,8-dinitropyrene (1,8-DNP) was compared with that of 4-nitroquinoline-1-oxide (4NQO) in cultured mouse lymphoma cells. L5178Y cells were grown in suspension culture and cloned in semisolid medium. 1,8-DNP and 4NQO were dissolved in dimethylsulfoxide (DMSO). DMSO alone had no effect on growth, cloning efficiency, or mutation frequency. Mutagenicity of test compounds was measured as the frequency of induction of resistance to 6-thioguanine (TG), methotrexate (MTX), ouabain (OUA), or 1-beta-D-arabinofuranosyl cytosine (ARA-C). Max mutation frequencies were obtained with 48-96-hr exposures for OUA, ARA-C, and MTX and with 144-192-hr exposures for TG. 1,8-DNP was not toxic at concentrations up to the max 2.5 ug/ml. Both 1,8-DNP and 4NQO produced dose-dependent increases in mutation frequencies in all mutation systems. Mutations evidently occurred by base-pair substitutions. Since previous studies had shown that 1,8-DNP produces frame-shift mutations in Salmonella and Escherichia coli, results suggest that 1,8-DNP produces mutations by different mechanisms in bacteria and mammalian cells. Problems of comparing mutagenicity of test chemicals when concentrations, treatment times, and toxicity are significantly different are discussed. (20 Refs)

12. INFLUENCE OF LIVER S-9 PREPARATIONS FROM RATS AND RAINBOW TROUT ON THE ACTIVITY OF FOUR MUTAGENS.

De Flora S, Zanacchi P, Bennicelli C, Arillo A
Inst. Hygiene, Sch. Medicine, Univ. Genoa, 16132 Genoa, Italy
Toxicol Lett; 10(4):345-349 1982

The effects of rat and trout liver post-mitochondrial fractions on benzo(a)pyrene (BP), 2-aminofluorene (2-AF), aflatoxin B1 (AFB1), and sodium dichromate in the Ames reversion assay were compared. Rat preparations were significantly more efficient in activating AFB1 and 2-AF. Rat and trout preparations were equally effective in decreasing the direct mutagenicity of sodium dichromate. Rat microsomes were virtually ineffective and trout preparations were slightly active in producing mutagenic metabolites from BP. (14 Refs)

INORGANIC AGENTS AND PARTICULATES INCLUDING FIBERS

13. DIRECT-ACTING MUTAGENS IN DIESEL EXHAUSTS: MAGNITUDE OF THE PROBLEM.

Rosenkranz HS
Center for Environmental Health Sciences, Case Western Reserve Univ., Sch. Medicine, Cleveland, OH, 44106
Mutat Res; 101(1):1-10 1982

Widespread and increased use of diesel engines in the United States will be accompanied by an increase in particulate emissions with potential mutagenic and carcinogenic components. The major class of chemicals associated with the mutagenic effect of diesel emissions (DE) is the nitroarenes, particularly the nitropyrenes. DE mutagenic activity is in the range of 15 revertants/ug dichloromethane extract which can be translated into approx 1.25 x 10(6) revertants/g particulate emitted. 1-Nitropyrene (NP) appears to be the major mutagenic species and accounts for approx 20% of the mutagenic activity in DE;. the other 80% of activity may be caused by 1,8-dinitropyrene (DNP). Diesel particulate containing 93 and 1.5 ug of NP and DNP, respectively, may account for the observed mutagenic potencies of DE materials. However, lower estimates for the DNP contribution to the total direct-acting mutagenicity of DE extract have been reported. The United States estimated annual output of NP is 14,415 kg, and of DNP is 233 kg. When heavy-duty diesels are considered, such estimates would be increased 2.4-fold to determine the total amount of nitropyrenes released yearly. Nitropyrenes are not only mutagenic, but are carcinogenic in rodents. Development of a postcombustion process to reduce the amounts of nitropyrene particulate in DE is feasible and warrants further study. Periodic, mandatory inspection of diesel-powered vehicles is advocated. (70 Refs)

14. CONTRIBUTION OF 1-NITROPYRENE TO DIRECT-ACTING AMES ASSAY MUTAGENICITIES OF DIESEL PARTICULATE EXTRACTS.

Salmeen I, Durisin AM, Prater TJ, Riley T, Schuetzle D
Engineering and Res. Staff, Ford Motor Co., P.O. Box 2053, Dearborn, MI, 48121
Mutat Res; 104(1-3):17-23 1982

The percentage contribution [P] of 1-nitropyrene [1-NP], a derivative of the carcinogenic polycyclic aromatic hydrocarbons, to the direct-acting Ames Salmonella assay mutagenicities of extracts of exhaust particles collected from three different diesel powered vehicles was assessed. 1-NP was shown to be a substantial contributor to the Ames assay mutagenicities for the three diesel particulate extracts examined. For Salmonella strains TA98, TA100, and TA1538, respectively, P was 16, approx 1, and 7% for one vehicle (1-NP = 2,030 +-220 ppm); 24, 9, and 17% for the second vehicle (1-NP = 150 +-30 ppm); and 13, 4, and 13% for the third vehicle (1-NP = 55 +-11 ppm). Using this assay system, even a 1% contribution of a single compound is important, considering the several hundreds of compounds present in the particulate extracts. Salmonella-histidine reversion assays indicated that the extract matrix had little effect on the mutagenicity of 1-NP. The significance of diesel exhaust-associated 1-NP in relation to adverse effects on human health was discussed. (22 Refs)

15. DIURNAL VARIATIONS IN THE MUTAGENICITY OF AIRBORNE PARTICULATE ORGANIC MATTER IN CALIFORNIA'S SOUTH COAST AIR BASIN.

Pitts JN, Harger W, Lokensgard DM, Fitz DR, Scorziell GM, Mejia V

Statewide Air Pollution Res. Center, Univ. California, Riverside, CA, 92521

Mutat Res; 104(1-3):35-41 1982

Diurnal variations in the mutagenicity of ambient particles collected simultaneously near downtown Los Angeles, California and at two downwind sites were examined to determine both the sources and ambient levels to which urban and suburban human populations may be exposed. Collections were made every 3 hr for a 24-hr period on two late summer days in 1980 and an early spring day in 1981 and assessed for mutagenicity using the Ames assay (using Salmonella strains TA98 and TA98NR). Ambient particulate mutagenicity displayed primary pollutant characteristics, responding both to vehicular emission rates and to atmospheric mixing ratios as shown by high correlation with CO, NOx and Pb levels. Results indicated that short-term peak mutagen densities can be much higher than the commonly reported 24-hr av. Nitroarenes may contribute substantially to the mutagenicity of ambient particulate matter in the study area. Chemical transformations of mutagenic material collected on the filters are apparently either very fast or very slow relative to the time scale used in these experiments. The increased contribution of promutagenic activity to the mutagenicity of the particles during periods of high emission rates, and its subsequent return to lower levels relative to direct activity, suggest that some promutagenic materials present in freshly emitted particulate organic matter are subject to rapid destruction in the atmosphere. (27 Refs)

16. COMPARISON OF THE GENOTOXIC ACTIVITIES OF EXTRACTS FROM AMBIENT AND FOREST FIRE POLLUTED AIR.

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Environ Mutagen; 4(1):37-43 1982

The genotoxicity of soluble, organic extracts of airborne organic particles was tested with use of the Salmonella reversion assay and the sister chromatid exchange (SCE) assay in cultured human lymphocytes. Airborne particles were collected in high volume air samplers in a non-industrial urban area under normal conditions (ambient) and during a period when dense smoke from a forest fire was carried by the wind into the area of the collectors. Salmonella strains TA98 and TA100 were used with and without Aroclor-induced rat liver S9 homogenate. While each sample caused increases in revertants in the Ames assay and increased incidence of SCE/cell, on the basis of the volume of air sampled, smoke-filled air induced 12-14x more bacterial reversions in TA100 and 16-38x more in TA98 than ambient (non-smoky) air. On a volume basis, 'smoky' air induced 43x more SCE in human lymphocytes than did ambient air. On the basis of extract weight, the 'smoky' air extract induced more SCE in human lymphocytes, but fewer bacterial revertants in the absence of S9 than the extract of 'nonsmoky' airborne particles. (17 Refs)

17. INDUCIBILITY OF SISTER-CHROMATID EXCHANGES BY HEAVY-METAL IONS.

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Mutat Res; 104(1-3):141-145 1982

Induction of sister-chromatid exchanges (SCE) by heavy metal ions was studied in Don Chinese hamster (DCH) cells in vitro. In each test 4 x 10(4) cells were incubated for 72 hr with 1 ml growth medium and a particular concentration of metallic compound. Cultures were exposed to 5-bromo-2'-deoxyuridine (BUdR) for two cell cycles (28 hr). Metal ions tested included Ti+++, Cr+++, Cr++++++, Fe++, Fe+++, Ni++, As+++, As+++++, Se++, Cd++, Sn++, and Hg++. Metallic compounds were dissolved in dimethyl sulfoxide. Median tissue culture inhibition doses (TCID50) were calculated by microscopic examination of fixed, stained cells. Rates of SCE were calculated for the TCID50 of each test ion. Spontaneous SCE occurred in untreated control cells at a rate of 3.90 +-0.82 SCE/metaphase. Any result greater than 5.4 SCE was considered to be a significant increase. Significant increases were produced by Cr+++, Cr++++++, Ni++, As+++, and As+++++. Cr++++++ produced a greater increase in SCE than did Cr+++. As+++ produced a greater increase in SCE than did As+++++. Although Se++ is a suspected carcinogen, increased SCE were not produced at TCID50. (17 Refs)

18. INCIDENCE OF NICKEL-INDUCED SISTER-CHROMATID EXCHANGE.

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Mutat Res; 101(1):67-75 1982

The incidence of nickel-induced sister-chromatid exchange (SCE) was studied in cultured human peripheral blood lymphocytes from a single donor. Nickelous chloride was added to cultures to a final concentration of 10(-3) to 10(-6) M. Control cells had a mean background incidence of 3.92 +-0.7 (standard error) SCE/cell. Addition of 1.19 x 10(-4) M nickel approx doubled the SCE incidence to 8.52 +-0.33 SCE/cell. Concentrations of nickel less than 1 x 10(-4) M yielded SCE values between 8.52 and 3.92/cell. Concentrations of 5 x 10(-4) M or more were lethal to human peripheral WBC. Chi-square analysis of the nickel response for variation in location of activity across the karyotype revealed no differences. More SCE were found in chromosomes 1 and 2 and those of Group B while fewer SCE were found in Group E, F, and G. The increased SCE frequency induced by nickel was statistically significant at the 99% confidence level and appeared to be of the same order of magnitude as chromium in Chinese hamster ovary cells. (20 Refs)

19. SOLUBILIZATION OF THE CARCINOGEN NICKEL SUBSULFIDE AND ITS INTERACTION WITH DEOXYRIBONUCLEIC ACID AND PROTEIN.

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Biochemistry; 21(4):771-778 1982

Significant concentrations (1-10 mM) of nickel(II) were found in soln after incubation of the potent carcinogen nickel subsulfide in 0.05 M Tris-HCl, pH 7.4, solutions containing DNA, rat liver microsomes, and NADPH. The presence of NADPH decreased the rate of solubilization of nickel subsulfide. The solubilized nickel exhibited electronic absorption spectra and magnetic moments characteristic of octahedral nickel(II). The solubilized nickel(II) bound to DNA with an apparent equilibrium constant of 730 M-1 and with a saturation binding value of one nickel per 2.4 nucleotides. Microsomes lowered the saturation binding of nickel to DNA but dramatically increased the amount of nickel-DNA complex stable to precipitation with salt and poly-(ethylene glycol). The amount of protein associated with DNA precipitated from protein-extracted solutions correlated with the amount of nickel bound to DNA. These results suggest that microsomes mediate the binding of nickel to DNA by forming a stable ternary protein-nickel(II)-DNA complex. (Author abstract) (60 Refs)

20. A REVIEW OF THE MUTAGENICITY OF CHROMIUM.

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Drug Chem Toxicol; 4(3):185-195 1981

Prokaryote testing for Cr(VI) gave the following results: (a) positive (frame-shift and base-pair) in Salmonella typhimurium strains TA1537, TA98, and TA100, while Cr(III) was negative at 100x as much; (b) Cr(VI) was positive (rec-effects) in Bacillus subtilis, while Cr(III) was negative; (c) Cr(VI) was positive (prototrophic revertants) in tryptophan auxotrophic strains of Escherichia coli and in E coli Hs30R. Eukaryotes testings gave for Cr(VI) positive (forward) results in Schizosaccharomyces pombe. In vitro Cr(VI) was: (a) positive (chromosomal variance) in Syrian hamster embryonic cells, while Cr(II) and (III) were negative at 7x as much; (b) Cr(VI) was positive (karyotypic damage) in mouse fetal cells, while Cr(III) was also positive; (c) Cr(VI) was positive (transformation) in BHK-21 fibroblast-like cells; (d) positive (chromosomal aberrations, CSA) in actively dividing human embryonal fibroblast and lymphocyte cells; (e) positive (CSA) in Chinese hamster ovary and embryonic cells; (f) positive (CSA) in human leukocytes, while Cr(III) was negative in heteroploidy except for expression of gap types of chromosomal variance; (g) Cr(VI) was positive (sister chromatid exchanges) in human fibroblasts and Chinese hamster ovary cells. In vivo Cr(VI) was positive (CSA) in unspecified mammals, and murine bone marrow showed nuclear fragments or micronuclei formation. (56 Refs)

21. TRACE METALS AND DISEASES.

Yamane Y, Sakai K
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Yuki Gosei Kagaku Kyokai Shi; 39(11):1105-1113 1981

Trace metal diseases (eg acrodermatitis enteropathica and Menkes' kinky-hair disease), diseases that cause abnormalities in metabolism of essential trace metals (eg Wilson's disease, cystic fibrosis, and hemochromatosis), assays of trace metals in biological fluids as diagnostic or prognostic aids in patients with cancer, and toxic trace metals were discussed. There are many influences that trace metals have on cancer. For example, pernicious anemia often accompanies various serious types of cancer and is related to iron, copper, and cobalt. Most patients with bronchial or some other lung cancers or transverse colon cancer have decreased serum levels of zinc, but patients with breast cancer or melanoma do not have decreased levels of zinc. Patients with primary osteosarcoma have lower copper/zinc ratios than normal subjects, and patients with metastatic osteosarcoma have copper/zinc ratios higher than normal subjects, suggesting a way to differentiate the two types of osteosarcoma. Compared to normal subjects, patients with breast cancer have 6-7x higher levels of total iron in breast tissue, patients with lung cancer have one fifth of the normal level of total iron in lung tissues, and patients with cancer of the transverse colon have normal levels of total iron in the colon tissue. Other studies have indicated the carcinogenic potential of toxic trace metals. (63 Refs) (In JPN)

22. REACTION OF CELLS CULTURED IN VITRO TO DIFFERENT ASBESTOS DUSTS OF EQUAL SURFACE AREA BUT DIFFERENT FIBRE LENGTH.

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Br J Exp Pathol; 63(1):109-115 1982

Peritoneal macrophages from mice were cultured in Leighton tubes and exposed to UICC chrysotile, crocidolite or amosite. Their cytotoxicity (Erythrosin uptake), release of lactate dehydrogenase (LDH) and uptake of 3H amino acids were determined according to wt (100 ug/tube), surface area (21.3 cm2) or fiber length. In all reactions tested chrysotile was more active than the amphiboles, but the latter gained activity if applied according to surface area. Uptake of 3H amino acids was, however, more marked in the case of the amphiboles, particularly on a wt basis. Long-fibered asbestos dusts proved more cytotoxic than the corresponding short fibers when used on the basis of equal mass. In experiments with ascites tumor cells induced by nemalite the different asbestos dusts showed a very significant reduction of 3H-labeled thymidine uptake, but on wt basis the amphibole uptake was markedly higher. (Author abstract) (17 Refs)

23. ASBESTOS-RELATED DISEASES.

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Clin Chest Med; 2(2):179-202 1981

Exposure to asbestos is associated with development of nonmalignant pleural diseases (pleural thickening, hyaline and calcified plaques, effusion), diffuse interstitial pulmonary fibrosis (asbestosis), diffuse malignant mesothelioma of the pleura and peritoneum, carcinoma of the lung, and possibly other neoplasms of other tissues. Types of asbestos minerals, chemical and physical properties, exposure, and biological effects of asbestos are reviewed. Epidemiology, pathology, clinical features, radiographic appearance, immunology, diagnosis, course, and prognosis of the various asbestos-related diseases are discussed. (226 Refs)

24. PLEURAL MESOTHELIOMA.

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Med Armees; 9(5):381-388 1981

Diagnosis and characteristics of pleural mesothelioma (PM) and the relation of PM to asbestos exposure are discussed. Thirteen cases of PM are described. PM produces pleural thickening with or without pleural effusion. Histologically, PM usually shows some combination of adenoid, endo-epithelial, and conjunctive cell differentiation. Diagnosis by cytologic examination of pleural fluid and by biopsy is difficult. Electron microscopic examination is usually able to show characteristic mesothelial cells. Asbestos exposure has been shown to be related to the development of pulmonary fibrosis, pleural hyaline deposits, pleurisy, bronchial cancer, and PM. A long delay exists between asbestos exposure and the development of PM. A brief, intense exposure to asbestos may be as dangerous as long term exposure. Various asbestos particles produce variable risks of PM. Mechanisms of asbestos carcinogenesis, types of exposure, use in construction and naval projects, and prevention of exposure also are considered. The most common manifestation of PM is pleurisy. Functional signs of PM include dyspnea and pain and less frequently, asthenia and cough. Clinical forms and progression of PM are described. Technics used in the diagnosis of PM include radiography, study of pleural liquid, pleuroscopy, pleural biopsy, thoracotomy, and tomodensitometry. (1 Ref) (In FRE)

25. IN VIVO AND IN VITRO EFFECTS OF CIGARETTE SMOKE ON CHROMOSOMAL DAMAGE AND SISTER-CHROMATID EXCHANGE IN HUMAN PERIPHERAL BLOOD LYMPHOCYTES.

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Mutat Res; 92(1/2):321-332 1982

The frequencies of chromosomal aberrations in phytohemagglutinin-stimulated peripheral blood lymphocytes (PBL) were studied in 49 women and 47 men (20-75 yr old); 55 were smokers (mostly in the light-to-moderate range, 1-10 cigarettes/day) and 41 were nonsmokers. The mean frequencies of all chromosomal aberrations combined were significantly higher in the smokers than in the nonsmokers (3.20 vs 2.22%). These differences were greatest for the frequencies of interchanges (0.22 vs 0.02%), gaps (0.56% vs 0.24%), fragments (0.67 vs 0.34%), dicentrics (0.42 vs 0.14%), and unambiguous exchange-type aberrations (0.64 vs 0.17%). A comparison of PBL cultures from a small group of subjects (3 nonsmokers, 3 heavy smokers) showed a 50% higher baseline frequency of sister chromatid exchanges (SCEs) in the smokers (means, 11.6 vs 7.6 SCEs/cell). Exposure to cigarette smoke condensate (CSC: 0.1-1.5 mg/10 ml) caused dose-dependent increases in SCE frequencies in the PBL of both smokers and nonsmokers. The dose-response curves were parallel, suggesting that the apparently greater effects of CSC in causing SCEs in the PBL of smokers simply reflected the higher basal SCE frequencies in this group, although the smokers' PBL showed somewhat more unscheduled DNA synthesis in response to CSC than the nonsmokers' PBL. Mitomycin C (10(-8)-10(-7) M) and ethyl methanesulfonate (10(-4)-10(-3) M) caused dose-dependent increases in the SCE frequencies in PBL from both smokers and nonsmokers. The parallel dose-response curves noted with both agents in both types of PBL suggested that the results reflected the basal differences in SCE frequencies between the groups, as opposed to a greater intrinsic sensitivity to mutagens in the PBL of smokers. (19 Refs)

26. DOUBLE-BLIND STUDY ON THE EFFECT OF CIGARETTE SMOKING ON THE CHROMOSOMES OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES IN VIVO.

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Mutat Res; 92(1/2):309-319 1982

The frequencies (expressed per 1,000 metaphases) of chromosomal aberrations (CAs) in peripheral blood lymphocytes (PBL) were studied in 170 smokers and 124 nonsmokers (all men) in a double-blind study. As compared to the nonsmokers, the smokers showed significantly higher mean frequencies of all CAs combined (2.01 vs 0.99), rings plus minutes (0.71 vs 0.24), chromatid translocations plus dicentrics (CT-D: 1.30 vs 0.67), and sister chromatid exchanges (SCEs: 5.78 vs 4.79). When subjects with histories of high alcohol consumption, several virus infections (including mumps), chronic drug treatment, and unusually high x-ray exposure were eliminated from the calculations, the CT-D frequencies in the PBL of smokers and nonsomokers (1.84 vs 0.83) were not significantly different, but the PBL of smokers continued to show a higher frequency of these CAs. The mean frequencies of second metaphases in 48-hr PBL cultures were significantly higher in the nonsmokers than the smokers (2.58 vs 1.74), indicating a depressive effect of smoking on phytohemagglutinin-induced lymphocyte stimulation. The mean frequencies of micronuclei in 3-day PBL cultures were the same in the smokers and nonsmokers (3.12 vs 2.97). It is concluded that structural CAs are better indicators of the cytogenetic effects of low-level chronic mutagen exposure in man than SCEs. (58 Refs)

27. MEMBRANE-BOUND SIALOGLYCOPROTEINS FROM RAT LIVER AFTER COMBINED EXPOSURE TO BENZO(A)PYRENE AND SULFUR DIOXIDE.

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Vopr Med Khim; 27(6):791-794 1981

The effect of carcinogens on metabolism of membrane-bound sialoglycoproteins (MBSGP) was studied in random-bred albino male rats. Animals were exposed to benzo(a)pyrene (BP) in combination with sulfur dioxide (SD). Within 2 wk, 6 wk, and 6 mo after exposure, rats were sacrificed and the distribution of MBSGP in the liver was determined. Combined exposure to BP and SD resulted in the increase of N-acetylneuraminic acid content in liver mitochondria and liver lysosomes, decrease of neuraminidase activity, and increase of beta-galactosidase activity. Carcinogens did not affect lipid peroxidation in the liver tissue. (20 Refs) (In RUS)

AMIDES, CARBAMATES AND UREAS

28. LONG-TERM FATE OF THE BILE DUCT CELLS PROLIFERATED DURING CHRONIC THIOACETAMIDE POISONING.

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Int J Tissue React; 4(1):55-61 1982

The proliferation of the bile duct cells of Sprague-Dawley rats, induced by a continuous feeding of thioacetamide (TAA: 0.05% solution in drinking water over a 4-mo period) was investigated. At the end of the exposure period, the liver was cirrhotic, with many bile duct proliferations surrounded by a small amount of connective tissues. Three types of cells were observed in the newly-formed ducts: bile duct cells similar in histochemistry to controls; highly specialized cells suggesting intestinal metaplasia; and poorly differentiated oval cells. All the neoformed bile duct cells stained positively for gamma-glutamyltranspeptidase (GGT) and negatively for butyrocholinesterase (BCE). By 1-2 mo after TAA withdrawal, most of the biliary proliferations disappeared. In those remaining, while the oval cells disappeared completely, the number of highly specialized cells had increased. The bile duct cells retained the same histochemical appearance, although some cells were now BCE positive. Five to 8 mo after TAA withdrawal, some large areas of cholangiofibrosis persisted within normal-looking tissue and the bile duct proliferations were surrounded by a remarkable amount of connective tissue. Most of the cells were PAS positive. The number of cells showing GGT activity decreased while the number staining for BCE increased. It is proposed that the normal-looking bile duct cells seen at the end of the TAA poisoning, but which slowly disappear during withdrawal, represent a reactive hyperplasia but have no role in the carcinogenetic process. The PAS positive cells, which remain during the recovery period within some cholangiofibrotic areas and exhibit strong BCE activity (characteristic of cholangiocarcinomas) may be considered preneoplastic. (15 Refs)

29. CONVERSION OF MALIGNANT MURINE EMBRYONAL CARCINOMAS TO BENIGN TERATOMAS BY CHEMICAL INDUCTION OF DIFFERENTIATION IN VIVO.

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Cancer Res; 42(5):1843-1849 1982

PCC4azal embryonal carcinoma tumors were grown in strain 129 mice by sc transplantation. When palpable, the tumors were treated with a combination of retinoic acid and dimethylacetamide. In vitro, this embryonal carcinoma cell line shows minimal spontaneous differentiation and is exquisitely sensitive to retinoic acid and/or dimethylacetamide induction of differentiation. Ten daily 20-ul intratumor injections of a solution of 10 mg retinoic acid per ml of dimethylacetamide resulted in nearly complete induction of morphological differentiation mainly into neuroepithelial and glandular derivatives. Control tumors showed minor spontaneous differentiation. Differentiation was associated with decreased tumor growth rate, decreased mitotic index, decreased extent of necrosis, and increased survival time of the hosts. In 4 of 18 cases, long-term survival of the hosts was effected by a complete differentiation of the malignant embryonal carcinoma tumors into benign teratomas. Retinoic acid:dimethylacetamide was also effective in inducing differentiation with the same dosage and schedule when administered systemically, ie, ip or sc. (Author abstract) (23 Refs)

30. ABSENCE OF SYNERGISM BETWEEN MUTAGENIC TREATMENTS, GIVEN ONE GENERATION APART, IN DROSOPHILA MELANOGASTER.

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Mutat Res; 92(1/2):117-121 1982

Drosophila melanogaster males were treated with ethyl methanesulfonate (EMS); their male offspring were treated with either EMS or urethan (UTH). The effects of the 2-generation treatm ent on the frequency of sex-linked recessive lethal mutations were no more than additive. When the first-generation males were treated with EMS or UTH and the F1 generation was untreated, the results suggested that both agents induced a loss of the ring-X chromosome in both post-meiotic and (pre)meiotic germ cell stages. UTH seemed to be very efficient in inducing sex chromosome loss, relative to recessive lethal induction, in mature spermatozoa. (12 Refs)

31. NEW ANTITUMOR IMIDAZOLE DERIVATIVE, 5-CARBAMOYL-1H-IMIDAZOL-4-YL PIPERONYLATE, AS AN INHIBITOR OF PURINE SYNTHESIS AND ITS ACTIVATION BY ADENINE PHOSPHORIBOSYLTRANSFERASE.

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Cancer Res; 42(3):1098-1102 1982

The mechanism of action of 5-carbamoyl-1H-imidazol-4-yl piperonylate (SL-1250) which has a broad antitumor spectrum, was examined by in vitro cell culture and enzymatic studies. In the serum-containing culture medium, SL-1250 was rapidly deacylated to 4-carbamoylimidazolium 5-olate (SM-108). Thus, SL-1250 might be acting on the cells in the form of SM-108. The growth of L5178Y cells was completely inhibited by 10(-5) M SL-1250. It should be noted that this growth inhibition was significantly reversed in the presence of equimolar concentrations of guanine, guanosine, or guanosine 5'-monophosphate to those of SL-1250. However, hypoxanthine and xanthine were not effective. These effects of purine addition were observed to be quite similar in growth inhibition by SM-108. It was found that inosine 5'-monophosphate dehydrogenase (EC 1.2.1.14; IMP dehydrogenase), a key enzyme of de novo purine synthesis, from Ehrlich carcinoma cells was inhibited by SM-108 only when 5-phospho-alpha-D-ribose 1-diphosphate (PRPP) and MgCl2 coexisted with SM-108. In contrast, a chemically synthetic ribonucleotide of SM-108 inhibited IMP dehydrogenase without PRPP and MgCl2, and the mode of inhibition was competitive with the Ki value of 2 x 10(-8) M. On the other hand, the inhibition of either growth of L5178Y cells or IMP dehydrogenase in the presence of PRPP and MgCl2 by these compounds was reversed by adenine. A nucleotide of SM-108 was chromatographically identified when [14C]SM-108 was incubated in the enzyme solution with PRPP and MgCl2. This conversion by enzyme was also inhibited by adenine. Viewed together, these results strongly suggest that SL-1250 is, after being converted to SM-108, activated to its nucleotide form by adenine phosphoribosyltransferase (EC 2.4.2.7) and that this SM-108 nucleotide blocks de novo synthesis of guanosine 5'-monophosphate by inhibiting IMP dehydrogenase. (Author abstract) (9 Refs)

32. EFFECT OF ORAL ADMINISTRATION OF PROTEASE INHIBITOR [N,N-DIMETHYLCARBAMOYLMETHYL 4-(4-GUANIDINOBENZOYLOXY)-PHENYLACETATE] METHANESULFATE ON THE GROWTH OF 3-METHYLCHOLANTHRENE-INDUCED CARCINOMA IN MICE.

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Gan; 73(1):108-110 1982

Oral administration of a synthetic protease inhibitor, [N,N-dimethylcarbamoylmethyl 4-(4-guanidinobenzoyloxy)-phenylacetate] methanesulfate, was used to challenge 3-methylcholanthrene-induced carcinoma. This drug was administered 3x daily via a stomach tube at doses of 12.5, 25 and 50 mg/kg in 33 mice harboring solid tumors. Oral administration of more than 50.0 mg/kg of this protease inhibitor significantly inhibited tumor growth and prolonged the survival time of cancer-harboring animals (p less than 0.05). These results indicate that oral administration of an inhibitor of kinin-forming protease has an antitumor effect on malignant tumors. (Author abstract) (7 Refs)

AMINO ACID ANALOGS AND MODIFIED NUCLEIC ACID CONSTITUENTS

33. IDUR INDUCTION OF A NEW TYPE OF RETROVIRUS-LIKE PARTICLE (EPSILON PARTICLE) IN TRANSFORMED FIBROBLASTIC MOUSE CELLS.

Lasneret J, Canivet M, Bittoun P, Peries J
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Ann Virol; 132(2):151-159 1981

Iododeoxyuridine (IdUr) induced a virus-like structure in fibroblastic BALB/c mouse cells transformed by the Kirsten strain of murine sarcoma virus (Ki-BALB cells). Confluent cultures were treated for 24 hr with 40 ug/ml IdUr and the cells were examined by electron microscopy at 24 and 48 hr post-treatment. No type C virus particles were observed in untreated control cells. IdUr-treated cells showed abundant budding and free C particles and a significant increase in the number of IA particles. A third virus-like particle was observed in treated cells. The structures were spherical with a diameter of 75-85 nanometers and were generally located in the cisternae of rough endoplasmic reticulum. The viral-like particles were observed in groups of 10 or more units and were sometimes intermixed with IA particles. Approx 5% of treated cells contained the particles. The particles were virtually identical to epsilon particles, named for the wheel-like intracisternal structures found in oocytes and early mouse embryos and resembling golden hamster R particles. (17 Refs)

34. THE INDUCTION OF SPECIFIC-LOCUS MUTATIONS AND SISTER-CHROMATID EXCHANGES BY 5-BROMO- AND 5-CHLORO-DEOXYURIDINE.

Heartlein MW, O'Neill JP, Pal BC, Preston RJ
Univ. Tennessee-Oak Ridge Graduate Sch. Biomedical Sciences, Oak Ridge, TN, 37830
Mutat Res; 92(1/2):411-416 1982

Chinese hamster ovary (CHO) cells were incubated for 25-32 hr with 5-bromo-2'-de oxyuridine (BUdR) or 5-chloro-2'-deoxyuridine. (ClUdR). Over the entire concentration range from 0.5-200 uM, both agents caused a dose-dependent increase in sister chromatid exchanges (SCEs) in the CHO cells. ClUdR induced 3-5x more SCEs than BUdR at the same concentration. Since ClUdR and BUdR showed similar levels of cytotoxicity and were incorporated into DNA to similar extents at a given concentration, the greater SCE-inducing capacity of ClUdR was attributed to the nature of the halogen substitution. Both agents (especially ClUdR) induced a high frequency of chromosome aberrations at greater than 100 uM. Both agents induced mutations to 6-thioguanine resistance (TGr) at greater than 50 uM. BUdR was consistently more mutagenic than ClUdR at the same concentration. Highly mutagenic concentrations of BUdR induced far fewer SCEs than induced by nonmutagenic concentrations of ClUdR. It is concluded that the mutagenic effects of BUdR and ClUdR are distinct from their SCE-inducing activities. These findings cast doubt on the practice of predicting mutation induction from studies designed to measure SCE frequency. (13 Refs)

35. MUTAGENICITY OF 5-AZACYTIDINE AND RELATED NUCLEOSIDES IN C3H/10T1/2 CLONE 8 AND V79 CELLS.

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Cancer Res; 42(3):817-823 1982

To determine whether 5-azacytidine (5-AzaCR)-induced transformation and/or differentiation of C3H/10T1/2 clone 8 (10T1/2) cells might have a mutational basis, we studied whether 5-AzaCR and structurally related nucleoside analogs could mutate 10T1/2 and Chinese hamster V79 cells. In an assay for mutation to ouabain resistance in 10T1/2 cells, which detects base substitution mutations but not frameshift mutations, 5-AzaCR and 6-azacytidine were not significantly mutagenic. 5-Aza-2'-deoxycytidine, 5-fluoro-2'-deoxycytidine, 5,6-dihydro-5-azacytidine, 5-fluoro-2'-deoxyuridine (FUdR), 5-bromo-2'-deoxyuridine (BUdR), and 1-beta-D-arabinofuranosylcytosine (ara-C) were only weakly mutagenic. In an assay for mutation to ouabain resistance in V79 cells, which also detects base substitution mutations but not frameshift mutations, 5-AzaCR, 5-aza-2'-deoxycytidine, FUdR, and ara-C were not detectably mutagenic, and BUdR was moderately mutagenic at highly cytotoxic concentrations. In an assay for mutation to 8-azaguanine resistance in V79 cells, which detects base substitution and frameshift mutations, 5-fluoro-2'-deoxycytidine and ara-C were weakly mutagenic, BUdR was moderately mutagenic at very cytotoxic concentrations, and 5-AzaCR, 5-aza-2'-deoxycytidine FUdR, 6-azacytidine, and 5,6-dihydro-5-azacytidine were not significantly mutagenic. Therefore, 5-AzaCR and related cytosine analogs can be considered as negligibly mutagenic. This study does not provide support for a mutational basis for 5-AzaCR-induced differentiation in 10T1/2 cells. Further, there was no correlation between the mutagenicity of the nucleosides 5-AzaCR, ara-C, BUdR, and FUdR studied here and their previously reported abilities to transform 10T1/2 cells. The mutagenicities of 5-AzaCR and FUdR were so low that the biological significance of these effects is uncertain. Hence, it is not clear to what extent, if any, mutation contributes to the transformation caused by these two compounds, and other possible mechanisms of transformation should also be investigated. (Author abstract) (49 Refs)

36. INACTIVATION OF S-ADENOSYLHOMOCYSTEINE HYDROLASE BY 9-BETA-D-ARABINOFURANOSYLADENINE IN INTACT CELLS.

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Dept. Pharmacology, Univ. Bergen, Sch. Medicine, MFH-bygget, Bergen, Norway
Cancer Res; 42(3):1130-1136 1982

The inactivation of S-adenosylhomocysteine hydrolase (EC 3.3.1.1) in isolated rat hepatocytes by 9-beta-D-arabinosuranosyladenine (ara-A) was associated with tight binding of ara-A to the enzyme and showed an initial phase obeying first-order kinetics characterized by KI (concentration of half-max rate of inactivation) of 12 uM for ara-A and a max rate of inactivation of 0.7 min-1. Two to 3% of the enzyme in rat hepatocytes was not available for inactivation. Similar results were obtained with some cultured cells, including mouse plasmacytoma cells (MPC-11), mouse fibroblasts (L-929), and human chronic myelogenic leukemia cells (K-562). In a cellular medium devoid of adenosine deaminase, inhibitors of this enzyme did not affect the inactivation process in rat hepatocytes and only slightly enhanced this process in the cultured cells (at low concentrations of ara-A). Inactivation of S-adenosylhomocysteine (AdoHcy) hydrolase in rat hepatocytes was associated with a massive build-up of AdoHcy (from 75 to 5,200 pmol/10(6) cells after 3 hr of incubation) and a moderate increase in cellular S-adenocylmethionine. The accumulation of AdoHcy in the cultured cells exposed to ara-A was less pronounced and no increase in cellular S-adenosylmethionine was observed. There was a quantitatively important export of AdoHcy from the rat hepatocytes and the cultured cells into the extracellular medium, whereas no leakage of S-adenosylmethionine was detected. The inactivation of AdoHcy hydrolase by ara-A in rat hepatocytes was inhibited in the presence of adenosine or homocysteine in the cellular medium. This effect of homocysteine correlated with increased cellular level of AdoHcy induced by this agent but was also associated with reduction in cellular uptake of ara-A. (Author abstract) (26 Refs)

37. INHIBITORY EFFECTS OF VARIOUS 5-HALOGENATED DERIVATIVES OF 1-BETA-D-ARABINOFURANOSYLURACIL 5'-TRIPHOSPHATE ON DNA POLYMERASES FROM MURINE CELLS AND ONCORNAVIRUS: SUBSTITUENT EFFECTS ON INHIBITORY ACTION.

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Lab. Viral Oncology, Aichi Cancer Center Res. Inst., Chikusa-ku, Nagoya 464, Japan
Biochemistry; 21(5):1019-1024 1982

The effects of four 5-halogenated derivatives of 1-beta-D-arabinofuranosyluracil 5'-triphosphate (aUTP) on the activity of DNA polymerases from mouse cells and oncornavirus were examined in comparison with that of the parent compound, aUTP, and also with those of the parent-related compounds, 5-alkylated derivatives of aUTP. The newly synthesized and tested compounds in this study were 1-beta-D-arabinofuranosyl-5-fluorouracil 5'-triphosphate (aFUTP), 1-beta-D-arabinofuranosyl-5-chlorouracil 5'-triphosphate (aClUTP), 1-beta-D-arabinofuranosyl-5-bromouracil 5'-triphosphate (aBrUTP), and 1-beta-D-arabinofuranosyl-5-iodouracil 5'-triphosphate (aIUTP). The results are summarized. Relationships between the chemical structures of the analogues and their inhibitory effects are discussed according to inductive, hydrophobic, and steric characteristics of the substituents on the 5 position of the uracil nucleus. It was concluded that both steric and hydrophobic effects of the halogen substituents were important for the inhibition of all DNA polymerases and that the inductive effect of halogen atoms was clearly observed for DNA polymerase beta with activated DNA and RLV DNA polymerase with (rA)n.(dT)12-18. (22 Refs)

38. CYCLIC NUCLEOTIDE MODULATION OF IN VITRO MORPHOLOGICAL TRANSFORMATION OF SYRIAN HAMSTER CELLS.

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Cancer Res; 42(4):1274-1278 1982

The cyclic nucleotides, cyclic adenosine 3':5'-monophosphate (cAMP) and cyclic guanosine 3':5'-monophosphate (cGMP) or their dibutyryl and monobrominated derivatives, may either increase or decrease morphological transformation of Syrian hamster embryo cells exposed to N-methyl-N'-nitro-N'-nitrosoguanidine (MNNG). The effect on transformation is primarily a function of the parent cyclic nucleotide and the duration of exposure to the nucleotides. At concentrations of 5 mM or larger for a minimum 24-hr exposure cAMP, cGMP, and their congeners reduced the colony-forming ability of non-transformed Syrian hamster embryo cells not exposed to MNNG; however, cGMP and its derivatives caused less toxicity than cAMP or its analogs. cAMP and its monobrominated and dibutyrylated derivatives decreased the transformation frequency associated with MNNG irrespective of whether the various adenylnucleotides were administered before or after MNNG. The greatest inhibitory effect on MNNG-induced transformation was obtained with N6,O2-dibutyryl cyclic adenosine 3':5'-monophosphate followed in order by 8-bromocyclic adenosine 3':5'-monophosp hate and cAMP. At equimolar doses, the dibutyryl and brominated analogs of cGMP but not unsubstituted cGMP enhanced transformation when administered prior to exposure of the Syrian hamster embryo cells to MNNG but reduced the transformation frequency when added after MNNG. The enhancing and inhibitory effects of the guanine cyclic nucleotide-induced alteration of MNNG-associated transformation frequencies were dose and time dependent and occurred in the order N6,O2-dibutyryl cyclic guanosine 3':5'-monophosphate greater than 8-bromocyclic guanosine 3':5'-monophosphate very much greater than cGMP. Butyric acid neither diminished nor increased MNNG-induced transformation frequency. The latter suggests that butyrate ions formed by metabolism of the cyclic nucleotide analogs were not a factor in the observed alterations of transformation frequency. (Author abstract) (35 Refs)

39. IS COFFEE DRINKING A HEALTH HAZARD?

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Sci Culture; 47(5):157-160 1981

Whether caffeine or its derivatives is a health hazard is discussed with respect to chemistry, metabolism, and mutagenicity testing. Evidence suggests that caffeine at low doses may act as a stimulator of the nervous system. High consumption, particularly in pathological conditions, may be hazardous. The dose of caffeine required for embryotoxicity is 100 mg/kg (equivalent to 40 cups of coffee). Mutagenicity testing has led to various conflicting results: caffeine has been found to be nonmutagenic, comutagenic, or a potent mutagen, particularly at high doses. (44 Refs)

40. EFFECT OF TEMPERATURE ON MUTATION IN CULTURED HUMAN SKIN FIBROBLASTS.

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Mutat Res; 92(1/2):417-426 1982

Normal human diploid skin fibroblasts were tested for mutation towards hypoxanthine guanine phosphoribosyltransferase (HPRT-) deficiency after exposure to different temperatures (31-40 C) in medium containing azaserine (AZS: HAT or HAT-adenine media). Cultivation in HAT medium (performed to delete preexisting mutants) was highly mutagenic. The results of some experiments suggested that AZS acted as an indirect mutagen. The process of AZS mutagenesis was highly temperature-dependent; the frequency of HPRT- mutants/cell generation increased 10x as the temperature was increased from 33-37 C. The temperature dependence, if used as a starting point for estimating the consequence of an increase in gonadal temperature, might be responsible for a 135% increase in incidence of the sex-linked lethal HPRT- disease (Lesch-Nyhan syndrome) in the human population. Available epidemiologic data on the frequency of Lesch-Nyhan syndrome and the ratio of paternal and maternal mutation leading to the disease do not contra dict the results on effects of temperature on mutation rate. (14 Refs)

ALIPHATIC HALOGEN COMPOUNDS

41. SPECIFICITY OF A PHENOBARBITAL-INDUCED CYTOCHROME P-450 FOR METABOLISM OF CARBON TETRACHLORIDE TO THE TRICHLOROMETHYL RADICAL.

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Biochem Pharmacol; 31(5):615-624 1982

Evidence is presented which demonstrates that the first polypeptide to disappear in liver microsomes of phenobarbital-induced rats treated with CCl4 was the 52,000 dalton P-450 cytochrome. Data are also presented which show that this form of cytochrome P-450 was capable of generating the trichloromethyl radical from CCl4 in a reconstituted system containing the purified cytochrome, NADPH-cytochrome P-450 reductase, NADPH, CCl4, and the spin-trapping agent, phenyl-t-butyl nitrone. Other cytochrome P-450 fractions not containing the 52,000 dalton form did not produce this radical. The formation of this highly reactive radical may have resulted in localized damage to the cytochrome, causing the cytochrome either to be released from the microsomal membrane or to form large aggregates which did not migrate in the gel electrophoretic procedures employed. (Author abstract) (30 Refs)

42. COVALENT BINDING OF CARBON TETRACHLORIDE METABOLITES TO THE HEME MOIETY OF CYTOCHROME P-450 AND ITS DEGRADATION PRODUCTS.

Fernandez G, Villarruel MC, De Toranzo EG, Castro JA
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Res Commun Chem Pathol Pharmacol; 35(2):283-290 1982

Trichloromethyl free radicals (CCl3*) produced during a benzoyl peroxide decomposition of CCl4 covalently bind to hemin. Enzymatically produced CCl3* by an NADPH anaerobic liver microsomal activation of CCl4, covalently binds to heme and heme degradation products from CO-binding particles. 14C from CCl4 covalently binds to heme and heme degradation products from liver CO-binding particles from rats treated with 14CCl4. In vivo covalent binding of 14CCl4 reactive metabolites to proteins from CO-binding particles is higher than that to the whole microsomal proteins. The possible correlation between binding of CCl3 to heme and protein moieties of P-450 and CCl4 induced P-450 destruction is discussed. (Author abstract) (17 Refs)

43. BINDING OF CHLOROFORM TO MOUSE AND RAT HEMOGLOBIN.

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Chem Biol Interact; 39(1):89-99 1982

The covalent binding of chemical carcinogens and mutagens to hemoglobin has been proposed as a dose monitor for environmental exposure. The binding of chloroform to hemoglobin in rats was demonstrated to result from the formation of addition adducts to amino acids in the globin. The altered amino acids were isolated with an amino acid analyzer employing ion exchange chromatography. The covalent binding of orally-administered [14C]chloroform to rat hemoglobin reached a peak within 10 hr. Afterwards, the amount of chloroform bound decreased slowly with half remaining at 7 wk. The extent of chloroform binding was linearly dependent upon dose between 0.1 and 100 umol/kg. Above 100 umol/kg chloroform the binding to hemoglobin increased at a reduced rate. The extent of [14C]chloroform binding resulting from either 10 daily dose of 0.1 umol/kg or a single 1.0 umol/kg was similar. The binding to hemoglobin in three strains of mice and rats varied from 85 +-7 umol/g Hb for Swiss (CFN) mice to 152 +-14 for Fisher-344 rats. We have demonstrated that the binding of chloroform to hemoglobin appears to have the following attributes of a dose monitor: (1) easily accessible from laboratory animals (and humans); (2) dose dependent; (3) stability, so that exposure can be determined weeks after it has ceased; (4) integration of low exposures which individually would be undetectable. (Author abstract) (15 Refs)

44. REVIEW OF EPIDEMIOLOGIC STUDY RESULTS OF VINYL CHLORIDE-RELATED COMPOUNDS.

Apfeldorf R, Infante PF
Office Carcinogen Identification and Classification, Health Standards, Programs, Occupational Safety and Health Admin. U. S. Dept. Labor, Washington, DC, 20210

Environ Health Perspect; 41:221-226 1981

Epidemiologic studies of structural analogs of vinyl chloride (VC) are reviewed. Analogs included epichlorohydrin (ECH), trichloroethylene (TCE), vinylidene chloride (VDC), ethylene dibromide (EDB), perchloroethylene (PCE), and carbon tetrachloride (CCl_4). Occupational and industrial uses of the compounds include manufacture of epoxy resins (ECH), copolymers and fibers (VDC), petroleum products (EDB), and pesticides (EDB). Other uses include metal degreasing (CCl_4, TCE, and PCE) and dry cleaning (PCE and formerly, TCE and CCl_4). Bioassays in experimental animals have demonstrated induction of tumors at multiple sites by EDB and CCl_4, in the respiratory tract by EDB and ECH, and in the liver by VDC, EDB, TCE, PCE, and CCl_4. Studies of workers exposed to ECH or dry cleaning solvents suggest an increased risk of lung cancer, but the increase is not significant, possibly due to sample size. Studies of workers exposed to the other compounds have not given positive evidence of carcinogenicity. All studies have been characterized by insensitivity to increases in mortality because of small sample size. In some studies workers were exposed to more than one suspected carcinogen, making interpretation of results difficult. Estimation of qualitative risk to humans due to specific compounds should be based on experimental animal studies rather than on human epidemiological studies. (17 Refs)

45. REVIEW OF EXPERIMENTAL CARCINOGENESIS BY COMPOUNDS RELATED TO VINYL CHLORIDE.

Chu KC, Milman HA
NCI, Bethesda, MD, 20205
Environ Health Perspect; 41:211-220 1981

Results in carcinogenicity studies of vinylidene chloride (VDC), trichloroethylene (TCE), tetrachloroethylene (PCE), 1,2-dichloroethane (DCE), 1,2-dibromoethane (DBE), and epichlorohydrin (EPC), all structural analogs of vinyl chloride (VC), are reviewed. Bioassays of carcinogenicity produced positive results with VDC in Swiss and CD-1 mice and CD and Sprague-Dawley rats. Nonpositive results were obtained with VDC in Fischer rats and B6C3F1 mice. TCE given by gavage or inhalation produced positive results in B6C3F1 mice. Nonpositive results were obtained with TCE in Sprague-Dawley and Osborne-Mendel rats. PCE given by gavage produced positive results in B6C3F1 mice and nonpositive results in Sprague-Dawley and Osborne-Mendel rats. DCE produced positive results in B6C3F1 mice and Osborne-Mendel rats when given by gavage but nonpositive results in Swiss mice and Sprague-Dawley rats when given by inhalation. DBE produced positive results by gavage in B6C3F1 mice and Osborne-Mendel rats. EPC produced positive results in male rats and was an initiator of carcinogenesis when administered sc. Results indicate that compounds thought to act directly without metabolic activation produce tumors at the site of administration, while those requiring activation do not. Important differences were found in response among species and strains. (21 Refs)

POLYHALOGENATED RING COMPOUNDS INCLUDING INSECTICIDES

46. MUTAGENICITY TESTING OF CHLORINATED BIPHENYLS AND CHLORINATED DIBENZOFURANS.

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Dept. Environmental Health, Univ. Cincinnati Medical Center, 3223 Eden Ave., Cincinnati, OH, 45267
Mutat Res; 101(1):45-56 1982

The Salmonella typhimurium/microsome assay of Ames was used to assay four chlorinated biphenyls and five chlorinated dibenzofuran compounds. None of the polychlorinated biphenyls (PCB: 4-chlorobiphenyl, 3,4,3',4'-tetrachlorobiphenyl, 2,4,2',4'-tetrachlorobiphenyl, and 2,4,6,2',4',6'-hexachlorobiphenyl) reverted any of the Salmonella tester strains, which included three DNA target sequences. Assays incorporating hepatic extracts (S9s) from rats treated with various inducing agents were also negative. Thus, S9 preparations from PCB-treated rats were not able to activate PCB components to detectably mutagenic forms in vitro. Dibenzofuran was assayed using dimethylsulfoxide as a solvent; the chlorinated derivatives were dissolved in a mixture of benzene:isooctane (1:9). Dibenzofuran, 2,9-dichlorodibenzofuran, 3,6-dichlorodibenzofuran, 2,3,7,8-tetrachlorodibenzofuran, and octachlorodibenzofuran were nonmutagenic for Salmonella strains TA98 and TA100 over a 3-log dose range with or without S9 activation. (37 Refs)

47. EFFECTS OF LONG-TERM INTAKE OF DDT ON RATS.

Cabral JR, Hall RK, Rossi L, Bronczyk SA, Shubik P
International Agency Res. on Cancer, 150 Cours Albert Thomas, 69372 Lyon Cedex 2, France
Tumori; 68(1):11-17 1982

DDT is a pesticide used in malaria-control programs throughout the world. Its potential carcinogenicity was studied in MRC Porton rats (Wistar-derived) which received dietary concentrations of 0, 125, 250 and 500 parts per million DDT (technical-grade) for life. The treatment had no adverse effects on body growth or survival rate. Various types of tumors were observed in animals in all groups: exposure to DDT resulted in statistically significant increased incidence of liver-cell tumors only in female treated rats; one such tumor was observed in control rats. No metastases of these tumors were found. (Author abstract) (30 Refs)

48. LACK OF CARCINOGENICITY OF DDT IN HAMSTERS.

Cabral JR, Hall RK, Rossi L, Bronczyk SA, Shubik P
International Agency Res. on Cancer, 150 Cours Albert Thomas, 69372 Lyon Cedex 2, France
Tumori; 68(1):5-10 1982

Syrian golden hamsters were fed for their lifespan a diet containing 0, 125, 250 and 500 parts per million (ppm) of DDT. The incidence of tumor bearing animals was 13% among control females and ranged between 11-20% in treated females. In control males 8% had tumors. The incidence of tumor bearing animals among treated males ranged between 17-28%. The incidence of adrenal cortex tumors showed a dose-related increase among the DDT-treated males. A liver-cell tumor and two liver hemangioendotheliomas were observed in three males treated with 250 ppm DDT. No liver-cell tumors were observed in the controls. No significant difference in tumor incidence was observed in treated vs control Syrian golden hamsters. (Author abstract) (28 Refs)

49. MUCINOUS GASTRIC HYPERPLASIA IN A COLONY OF RHESUS MONKEYS (MACACA MULATTA) INDUCED BY POLYCHLORINATED BIPHENYL (AROCLOR 1254).

Geistfeld JG, Bond MG, Bullock BC, Varian MC
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Lab Anim Sci; 32(1):83-86 1982

Since 1971, 45 of 259 male rhesus monkeys housed in a primate building have died of a chronic and progressive disease characterized by diarrhea, dehydration, weakness, gingivitis, emaciation, and alopecia. The principal necropsy finding in these monkeys, and in eight others killed for experimental purposes, was hypertrophic and hyperplastic mucinous gastropathy involving both the mucosa and submucosa. The toxic agent involved was identified as the polychlorinated biphenyl (PCB), Aroclor 1254. The suspected source of the toxic agent was a concrete sealer used during building construction. (Author abstract) (14 Refs)

50. PURIFICATION AND CHARACTERIZATION OF A SECOND FORM OF HEPATIC CYTOCHROME P-448 FROM RATS TREATED WITH A PURE POLYCHLORINATED BIPHENYL ISOMER.

Goldstein JA, Linko P, Luster MI, Sundheimer DW
Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709
J Biol Chem; 257(5):2702-2707 1982

A new form of cytochrome P-448 has been isolated from livers of rats treated with 3,3',4,4',5,5'-hexachlorobiphenyl (HCB). The purified cytochrome (referred to as P-448HCB) had a specific content of 18.8 nmol of cytochrome/mg of protein and migrated as a single band on sodium dodecyl sulfate-polyacrylamide gels. The major forms of cytochrome P-450 induced by phenobarbital and 3-MC (referred to as P-450PB and P-450MC, respectively) were also purified for comparative studies. Although cytochrome P-448HCB has a mol wt similar to that of cytochrome P-450PB, these cytochromes differ in their spectral properties, chromatographic behavior, and peptide maps after limited proteolysis. Cytochrome P-448HCB clearly differs from cytochrome P-448MC in its mol wt, chromatographic behavior, and peptide maps. The oxidized spectra of cytochromes P-448MC and P-448HCB are also distinctly different. Oxidized cytochrome P-448HCB has absorbance maxima at 393 and 648 nm, indicating that this form is a high spin ferric hemoprotein. In contrast, cytochrome P-448MC has a Soret max at 418 nm, indicative of the low spin state. Antisera against cytochrome P-448HCB gave a single precipitin band against its antigen in Ouchterlony double diffusion plates but did not cross-react against cytochrome P-450PB. A faint cross-reaction against cytochrome P-448 was observed. This cross-reaction could be removed by immunoabsorption with partially purified cytochrome P-448MC indicating that the three hemoproteins have different immunological properties. (29 Refs)

51. EFFECTS OF POLYCHLORINATED BIPHENYLS AND ENVIRONMENTAL TEMPERATURE ON IN VITRO FORMATION OF BENZO[A]PYRENE METABOLITES BY LIVER OF TROUT (SALMO GAIRDNERI).

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Biochem Pharmacol; 31(4):561-566 1982

Rainbow trout (Salmo gairdneri) held at 7 C and 16 C were given Aroclor 1254 (PCB) (10 mg/kg body wt) via ip injections. The binding of [3H] benzo[a]pyrene (BaP) to deproteinized salmon sperm DNA was assayed (pmoles BaP equivalents per mg DNA per mg protein) using the post-mitochondrial supernatant (S 10) fractions from livers of fish at 24-168 hr after the PCB exposure. Liver enzymes from the untreated fish acclimated at 7 C yielded an av binding value (0.37 +-0.17) which was significantly greater (p less than 0.05) than the value (0.07 +-0.03) for untreated fish at 16 C. Liver supernatant fractions from PCB-induced fish acclimated at 16 C and sampled at 24-120 hr showed a substantial increase (p less than 0.05) in the binding (av value 2.4 +-1.8) compared to the value obtained with untreated fish at 16 C. At 24, 48 and 120 hr after the PCB treatment of fish held at 7 C, there was no significant increase in the binding value or extent of metabolism of BaP compared to that obtained with the untreated fish at 7 C. However, at 168 hr, three of four fish at 7 C responded to the PCB treatment with significantly (p less than 0.05) increased binding values (3.3 +-1.6). Chromatographic analyses of the ethyl acetate-soluble metabolites revealed that 3-hydroxy BaP and 7,8-and 9,10-dihydrodiols were the major metabolites; K-region metabolites were formed in trace amounts in untreated and PCB-treated fish at both temperatures. No marked qualitative differences were observed in metabolite profiles after the PCB treatment; however, overall metabolism of BaP and production of reactive metabolites by liver enzymes were considerably (p less than 0.05) enhanced in the PCB-induced fish at both 7 C and 16 C. (Author abstract) (42 Refs)

52. MUTAGENIC AND ALKYLATING ACTIVITIES OF 3-METHYL-1-PHENYLTRIAZENES AND THEIR POSSIBLE ROLE AS CARCINOGENIC METABOLITES OF THE PARENT DIMETHYL COMPOUNDS.

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Cancer Res; 42(4):1446-1453 1982

The compound 3-methyl-1-phenyltriazene and a series of ring-substituted derivatives (4-methylphenyl, 4-chlorophenyl, and 2,4,6-trichlorophenyl), structurally related benzenediazonium fluoborates and phenyl azides, as well as the recently isolated [1-methyl-3-(2,4,6-trichlorophenyl)-2-triazeno]methyl beta-D-glucopyranoside uronic acid, were studied for their mutagenic activity in Salmonella typhimurium strains. Of these compounds, the 3-methyl-1-phenyltriazene derivatives and 2,4,6-trichlorobenzenediazonium fluoborate were found to be direct-acting mutagens; the glucuronide was active in strain TA 1530 only after deconjugation with beta-glucuronidase. The half-lives of the monomethylphenyltriazenes in vitro were determined and compared with their methylating activity towards 4-(4-nitrobenzyl)pyridine and their mutagenicity. The results are discussed in relation to the possible mechanism of action of the N,N-dimethylphenyltriazenes and their monomethyl derivatives as mutagens and organ-specific carcinogens. (Author abstract) (43 Refs)

53. CHRONIC TOXICITY OF METRIFONATE.

Machemer L
Inst. Toxicology, Bayer AG, Wuppertal, Elberfeld, W. Germany
Acta Pharmacol Toxicol [Suppl] (Copenh); 49(5):15-28 1981

From chronic toxicity studies with metrifonate (identical with trichlorfon) on different animal species, the following conclusions can be reached: (1) There is no conclusive evidence that trichlorfon has a carcinogenic effect. (2) There is no indication that trichlorfon has a significant cumulative toxic effect. (3) There is no confirmation that trichlorfon has a specific effect on liver, blood and hematopoietic organs. (4) The toxicological profile of trichlorfon in the chronic toxicity study consists, on the one hand, in a depression of cholinesterase activity whereby the different animal species differed in their sensitivity. In rats, cholinesterase activity was depressed in serum at dietary levels of 500 ppm and above and also in erythrocytes at a dietary concentration of 1,000 ppm. In dogs, cholinesterase activity was depressed in serum and erythrocytes at a dietary level of only 200 ppm. The Rhesus monkey seemingly is very sensitive because erythrocyte cholinesterase activity is possibly reduced at a daily dose of 0.2 mg/kg per os. On the other hand, induction of an inhibition of spermatogenesis in rats and dogs at a high dose level is discussed, an effect which seemingly is morphologically detectable but nonetheless seems not to affect function as animal experiments have demonstrated. (Author abstract) (21 Refs)

54. METHODS FOR THE RECOVERY OF ORGANIC CARCINOGENS FROM WATER.

Ehrlich K, Cawley G, Klein E
Gulf South Res. Inst., New Orleans, LA
Sci Tech Aerosp Rep; 19(24):3372 1981

The organic carcinogens benzo(a)pyrene, dieldrin, and N-acetyl-2-aminofluorene were recovered on XAD-2 macroreticular resin in yields of 90% or more from distilled water or seawater or in yields of 40% or more from Lake Pontchartrain water containing a high concentration of organic material. The original solutions contained less than 500 parts per trillion of carcinogen. These results show that XAD-2 provides an efficient means for recovering nonpolar organic carcinogens from dilute solutions. (Author abstract) (no Refs)

55. MUTAGENICITY OF HPLC FRACTIONS FROM EXTRACTS OF AATREX-TREATED CORN.

Singh I, Lusby AF, McGuire PM
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Environ Mutagen; 4(1):45-53 1982

Water-imbibed kernels of hybrid corn were incubated in water containing 0, 30, 60 and 90 ppm of the herbicide AAtrex (80W), the active ingredient of which is atrazine (2-chloro-4-ethylamino-6-isopropylamino-s-triazine). At the 3-leaf stage, the plants were harvested and homogenized in five volumes of distilled water. The homogenate was filtered and centrifuged at 2,500 x gravity for 10 min. The crude extracts were tested for induction of gene conversion in a diploid (D4) strain of Saccharomyces cerevisiae heteroallelic at two loci; the strain requires adenine and tryptophan for growth. The extracts were subject ed to analysis by high pressure liquid chromatography, and fractions collected in water, 50% and 100% methanol were similarly analyzed. AAtrex alone did not induce conversion. There was a clear dose response at both loci with the 50% methanol extract, indicating that some of the mutagenic activity resulted from interaction between the plant and herbicide. The 50% methanol fraction induced more conversion at 10 mg/ml than did the crude extract at twice the concentration. The study indicates that AAtrex-treated germinating corn contains more mutagen than controls. (44 Refs)

56. STUDIES ON THE MUTAGENIC POTENTIAL OF THE PESTICIDE CHLORDIMEFORME AND ITS PRINCIPAL METABOLITES IN THE MOUSE HERITABLE TRANSLOCATION ASSAY.

Lang R, Adler ID
Res. Lab., Schering, Berlin/Bergkamen, W. Germany
Mutat Res; 92(1/2):243-248 1982

Random-bred NMRI/SPF male mice were treated for 7 wk (by gavage) with max tolerated doses of chlordimeforme (CDMF: 120 mg/kg/day) or one of its principal metabolites, N-formyl-4-chloro-o-toluidine (100 mg/kg/day) and 4-chloro-o-toluidine (200 mg/kg/day), then mated with untreated females. The treated mice and male F1 offspring were screened for fertility. Animals showing reduced fertility or sterility were examined cytogenetically, by scoring meiotic chromosomes for translocation multivalents or assessing mitotic cells for marker chromosomes. CDMF and both of its principal metabolites at toxic doses did not induce translocation heterozygosity. The positive control agent, triethylene melamine (0.05 mg/kg/day), gave the expected mutagenic response. (7 Refs)

57. AN EVALUATION OF THE GENOTOXIC PROPERTIES OF INSECTICIDES FOLLOWING PLANT AND ANIMAL ACTIVATION.

Gentile JM, Gentile GJ, Bultman J, Sechreist R, Wagner ED, Plewa MJ
Dept. Biology, Hope Coll., Holland, MI, 49423
Mutat Res; 101(1):19-29 1982

Commercial grades (CG) and technical grades (TG) of two carbamate, six organophosphate, and two chlorinated hydrocarbon insecticides were tested for genotoxicity in Salmonella typhimurium and Saccharomyces cerevisiae with rat liver metabolic activation (S9), plant metabolic activation (maize 1S fractions), or no activation. CG of each insecticide was also tested for mutations at the waxy (wx) locus of Zea mays. Carbofuran, metham, curacron, phorate, and chlorpyrifos were negative in all assays. CG and TG fonofos were mutagenic to Salmonella following S9 activation and TG fonofos was weakly positive in the S cerevisiae assay. TG terbufos was recombinogenic in S cerevisiae both directly and with S9 activation, while CG was weakly recombinogenic when tested directly. Field formulation of ethoprop was mutagenic in the maize wx assay. TG heptachlor was mutagenic to Salmonella with S9 activation. Both CG and TG chlordane were recombinogenic to Saccharomyces following S9 activation. Both heptachlor and chlordane were genotoxic following 1S activation and both were mutagenic in the maize wx assay. Mammalian microsomal activation systems should be complemented with plant activation systems in order to provide a comprehensive analysis of the genotoxic potential of agricultural agents. (26 Refs)

58. ALKYLATING PROPERTIES OF DICHLORVOS (DDVP).

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Dept. Radiobiology, Wallenberg Lab., Univ. Stockholm, S-106 91 Stockholm, Sweden
Acta Pharmacol Toxicol [Suppl] (Copenh); 49(5):56-66 1981

Dichlorvos (DDVP) is a methylating agent. In DNA from mice given 1.9 x 10(-6) mol/kg of DDVP, a degree of alkylation of guanine-N-7 amounting to 8 x 10(-13) mol methyl per g DNA, was found. From this, a rate of clearance of 29 hr-1 was estimated. This value is in reasonable agreement with the value

(55 hr(-1)), calculated from published data on the concentration over time of DDVP in the brain after injection of the compound in mice. Applying a risk estimation on humans exposed to DDVP, the genetic risk connected with the methylating activing of DDVP is low or very low. Comparing the mutagenic effectiveness of DDVP with that of methyl methanesulfonate, indicates that DDVP is more effective than expected from reaction kinetic data. The possible contribution of the dichloroacetaldehyde formed in vivo from DDVP has to be evaluated before a complete risk estimate can be made for DDVP. (Author abstract) (46 Refs)

59. ALKYLATION OF DNA BY ORGANOPHOSPHORUS PESTICIDES.

Wooder MF, Wright AS
Shell Toxicology Lab., Shell Res. Limited, Sittingbourne Res. Center, Sittingbourne, Kent, ME9 8AG, England
Acta Pharmacol Toxicol [Suppl] (Copenh); 49(5):51-55 1981

Methods for the detection of in vivo alkylation of nucleic acids are discussed. Alkylation of mammalian DNA at N-7 of guanine provides the most sensitive and least equivocal evidence of methylation by an exogenous chemical or its metabolite. No 7-methylguanine was detected in the combined DNA from the lungs, livers, hearts, brains, kidneys, testes and spleens from 20 rats exposed to 0.064 ug l-1 of [Me-14C]-dichlorvos at a specific radioactivity of 113 Ci mol-1 for 12 hrs. (Author abstract) (7 Refs)

BENZENE DERIVATIVES

60. EFFECT OF STYRENE ON HEPATIC MIXED FUNCTION OXIDASES, GLUTATHIONE CONTENT AND GLUTATHIONE-S-TRANSFERASE ACTIVITY IN RATS.

Das M, Dixit R, Mushtaq M, Srivastava SP, Seth PK
Industrial Toxicology Res. Centre, Mahatma Gandhi Marg, P.O. Box 80, Lucknow-226001, India
Drug Chem Toxicol; 4(3):219-227 1981

Adult male albino rats given 7 consecutive daily doses of styrene at 270, 450, or 900 mg/kg were assayed for changes in their hepatic enzymes on the 8th day. Glutathione was suppressed at the highest dose, while glutathione-S-transferase was suppressed at the middle and highest doses. Both higher doses elevated arylhydrocarbon hydroxylase, aniline hydroxylase, aminopyrine-N-demethylase, and ethylmorphine-N-demethylase. These results implicate styrene as a potential enhancer of polycyclic aromatic hydrocarbon carcinogenicity. (14 Refs)

61. INVESTIGATION OF STYRENE IN THE LIVER PERFUSION/CELL CULTURE SYSTEM. NO INDICATION OF STYRENE-7,8-OXIDE AS THE PRINCIPAL MUTAGENIC METABOLITE PRODUCED BY THE INTACT RAT LIVER.

Beije B, Jenssen D
Div. Cellular Toxicology, Environmental Toxicology Unit, Univ. Stockholm, Wallenberg Lab., S-10691 Stockholm, Sweden
Chem Biol Interact; 39(1):57-76 1982

Mutagenic effect of styrene and styrene-7,8-oxide was studied with the isolated perfused rat liver as metabolizing system and Chinese hamster V79 cells as genetic target cells. Styrene-7,8-oxide which is mutagenic per se was rapidly metabolized by the perfused rat liver. Thus no mutagenic effect was detected either in the perfusion medium or in the bile. However when styrene was added to the perfusion system, an increase in V79 mutants was observed regardless of where in the circulating perfusion medium the V79 cells were placed: the same effect was obtained with V79 cells close to the liver as well as at a distance from the liver. No mutagenic effect was observed in the bile. Simultaneous analysis of the styrene-7,8-oxide concentration in the perfusion medium, suggest that this metabolite is not the cause of the mutagenic effect observed during perfusion with styrene. The effect of the two test compounds on some liver functions was also studied. It is suggested that the results on styrene and styrene-7,8-oxide found here using the liver perfusion/cell culture system mimic the metabolism expected to be found in the intact animal, thus indicating that styrene-7,8-oxide is not the principal mutagenic metabolite of styrene in vivo. (42 Refs)

62. STUDIES ON METABOLISM AND TOXICITY OF STYRENE. IV. 1-VINYLBENZENE 3,4-OXIDE, A POTENT MUTAGEN FORMED AS A POSSIBLE INTERMEDIATE IN THE METABOLISM IN VIVO OF STYRENE TO 4-VINYLPHENOL.

Watabe T, Hiratsuka A, Aizawa T, Sawahata T, Ozawa N, Isobe M, Takabatake E
Lab. Drug Metabolism and Toxicolgy, Dept. Hygienic Chemistry, Tokyo Coll. Pharmacy, 1432-1 Horinouchi, Hachioji-shi, Tokyo 192-03, Japan
Mutat Res; 93(1):45-55 1982

The role of 1-vinylbenzene 3,4-oxide (VBO) in the metabolism of styrene to 4-vinylphenol and the mutagenicity of VBO in Salmonella typhimurium strains were studied. VBO had a half-life of 4.3 sec at pH 7.4 in aqueous soln. VBO was toxic to TA98 and TA100 strains, but was mutagenic only in TA100. VBO induced 7233 His+ revertant colonies/plate at a dose of 1.0 micromoles/plate. VBO was shorter-lived and more mutagenic than the 1,2-oxide. The vinylphenols formed from VBO and the 1,2-oxide were neither mutagenic nor cytotoxic. (24 Refs)

63. EFFECT OF BENZENE METABOLITES ON PHYTOHEMAGGLUTININ-STIMULATED LYMPHOPOIESIS IN RAT BONE MARROW.

Pfeifer RW, Irons RD
Dept. Pathology, Chemical Industry Inst. Toxicology, Research Triangle Park, NC
J Reticuloendothel Soc; 31(2):155-170 1982

Chronic exposure of animals to benzene results in lymphocytopenia and bone marrow depression. A highly sensitive microculture system was developed to amplify and characterize marrow mitogen response which depended on the isolation of cells by Percoll continuous density gradient centrifugation and strict adherence to optimal culture conditions. Maximal mitogen responses to phytohemagglutinin (PHA) and concanavalin A (con A), as assessed by (3H)-thymidine uptake, occurred at later times in rat bone marrow cultures (Days 5-7 of culture) compared with spleen and thymus (Days 2-3). Compared with spleen and thymus, the PHA:con A stimulation ratio was inverted for marrow, yet the responsive cells were morphologically identical to those of peripheral lymphoid organs. Populations enriched in lymphoid precursors were inhibited from responding to PHA stimulation at noncytotoxic concentrations (greater than uM) of the benzene metabolites, p-benzoquinone or 1,2,4-benzenetriol. Pretreatment with less than uM concentrations of metabolites resulted in a modulation of lectin-induced responses such that blastogenesis was induced at higher concentrations of lectin relative to untreated cells. These changes indicate that known metabolites of benzene induce a concentration dependent modulation of differentiation and proliferation in lectin-stimulated cells from rat bone marrow in vitro. (Author abstract) (56 Refs)

DRUGS, COSMETICS, DETERGENTS AND OTHER COMMERCIAL MATERIALS

64. EXCESS LUNG CANCER RISK IN A SYNTHETIC CHEMICALS PLANT.

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Environ Health Perspect; 41:159-165 1981

The occurrence of lung cancer among workers employed at a synthetic chemicals plant at any time during the period 1942-1973 retrospective cohort study included 4,806 males. Of these, 4,174 were alive at the time of the study and 73 were lost to follow-up but assumed to be alive. At the end of the period studied only 30% of the cohort would have been greater than 54 yr old; 63% had the opportunity to achieve 20 yr latency. When all employees were considered to be at risk from the start of employment at the plant, the standardized mortality rate (SMR) was significantly elevated for malignant neoplasms of the CNS (SMR 209) and respiratory system (SMR 149). When employees were considered at risk only after 10 yr of employment, results were similar but the SMR was slightly higher. Excess lung cancers were not due solely to exposure to vinyl chloride (VC). A case-comparand study of 27 workers with lung cancer indicated that large-cell undifferentiated type lung cancer (LCLC) occurred more frequently among workers (30%) than among comparands from the community (10%) with lung cancer. Among workers the risk of lung cancer was primarily for LCLC and adenocarcinoma. Analysis of exposure to various chemicals using a serially additive expected dose model indicated poly(vinyl chloride) dust as the most likely etiological agent. The next most likely agent was vinylidene chloride. Latency time peaked at 5-16 yr. (27 Refs)

65. NEOPLASTIC AND NONNEOPLASTIC EFFECTS OF VINYL CHLORIDE IN MOUSE LUNG.

Suzuki Y
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Environ Health Perspect; 41:31-52 1981

Carcinogenicity of vinyl chloride (VC) was studied in the lungs of CDI Charles River white strain mice. Of 27 mice, 6 were exposed to VC (2,500 or 6,000 ppm) for 5 hr/day, 5 days/wk for 5 mo and killed after a 6-day period without treatment. Thirteen mice were exposed to VC (2,500 or 6,000 ppm) for 6 mo and killed 2 days after the end of treatment. Eight mice were exposed to VC (2,500 or 6,000 ppm) for 6 mo and killed after a 37-day recovery period. The effects of lower doses (0, 1, 10, or 100 ppm, 5 hr/day, 5 days/wk for 4 wk) were studied in 120 mice. Pulmonary tumors were found in 26/27 mice treated with the higher doses. Tumors were multiple and either tubulo-papillary or adenomatous. No metastases were found. Electron microscopy showed short microvilli, tight junctions between adjacent cells, osmiophilic lamellar bodies, large irregular mitochondria, well-developed Golgi complexes, continuous or discontinuous basement membranes, occasional sequestration of crystalloids, and lack of cilia and secretory granules. Tumors were classified as alveologenic, possibly developing from hyperplastic Type II alveolar epithelium. Nonneoplastic effects included proliferation and hypertrophy of bronchiolar cells, abnormal mitochondria, and proliferation of rough endoplasmic reticulum. Low doses of VC produced tumors in 5/9 mice at 100 ppm, 2/9 at 10 ppm, 1/9 at 1 ppm, and 0/10 at 0 ppm. Results indicate that VC induces pulmonary tumors in mice in a dose-related fashion; mouse lung is a sensitive indicator of VC carcinogenicity. (52 Refs)

66. CANCER INDUCTION FOLLOWING SINGLE AND MULTIPLE EXPOSURES TO A CONSTANT AMOUNT OF VINYL CHLORIDE MONOMER.

Hehir RM, McNamara BP, McLaughlin J, Willigan DA, Bierbower G, Hardisty JF
U. S. Consumer Product Safety Commission, Westwood Towers Build-[illegible], Room 738, 5401 West Blvd., Washington, DC, 20207
Environ Health Perspect; 41:63-72 1981

The effects of total dose and frequency of exposure on carcinogenesis of vinyl chloride monomer (VCM) were studied in Fischer 344 and Sprague-Dawley rats and A/J and ICR mice. Fischer rats and ICR mice were exposed to a single dose of 50, 500, 5,000, or 50,000 ppm VC for 1 hr. Fischer rats and A/J mice were exposed 10x to 500 ppm VCM (1 hr/day, 5 day/wk for 2 wk) or 100x to 50 ppm (1 hr/day, 5 days/wk for 20 wk). Sprague-Dawley rats were exposed to 50-500 ppm VC (1 hr/day, 5 days/wk for 10 wk). All test animals were observed until sacrifice (18-24 mo). Animals were killed when moribund or on schedule. Significant toxic effects were observed only at 50,000 ppm. VCM produced dose-related increases in the frequency of pulmonary adenomas and carcinomas in mice at concentrations of 5,000 and 50,000 ppm. Multiple exposures of A/J mice to 500 ppm produced significant increases in occurrence of pulmonary adenomas and carcinomas. Multiple exposures to 50 ppm did not produce significant increases in occurrence of the tumors. Carcinogenic effects were not observed in rats at the total VCM doses used. Results indicate that carcinogenesis depends on total dose but concentration may be the most critical factor in short-term exposure. Single exposure required at least 5,000 ppm-hr in mice or 50,000 ppm-hr in rats for carcinogenesis. Mice were more sensitive than rats to VCM. (10 Refs)

67. EFFECT OF ETHANOL ON VINYL CHLORIDE CARCINOGENESIS.

Radike MJ, Stemmer KL, Bingham E
Dept. Environmental Health, Kettering Lab., Univ. Cincinnati Medical Center, 3223 Eden Ave., Cincinnati, OH, 45267
Environ Health Perspect; 41:59-62 1981

The potential cocarcinogenicity of ethanol with vinyl chloride (VC) was studied in male Sprague-Dawley rats. A total of 320 rats (80 rats in each of four groups) were studied: Group 1 was exposed to VC (600 ppm, 4 hr/day, 5 days/wk for 1 yr), Group 2 was exposed to VC and ethanol (5% in water, beginning 4 wk before the start of VC exposure and continuing for life), Group 3 was exposed only to ethanol, and Group 4 was exposed only to filtered air. At 18 mo rats exposed to VC showed an av weight loss of approx 9%. At 18 mo the survival rate was 40% for Group 1, 18% for Group 2, 73% for Group 3, and 70% for Group 4. Angiosarcomas were found in 23% of Group 1, 50% of Group 2, and 0% of Groups 3 and 4. Hepatocellular carcinomas were found in 44% of Group 1, 60% of

Group 2, 10% of Group 3, and 0% of Group 4. Lymphosarcomas were found in all groups but most frequently in Group 2. Endocrine tumors were found in 57 rats in Group 3, compared with 29 in Group 1, 30 in Group 2, and 8 in Group 4. Some rats developed more than one angiosarcoma or carcinoma. Results indicate that ethanol has a strong cocarcinogenic effect in rats exposed to VC. (8 Refs)

68. CARCINOGENICITY BIOASSAYS OF VINYL CHLORIDE MONOMER: A MODEL OF RISK ASSESSMENT ON AN EXPERIMENTAL BASIS.

Maltoni C, Lefemine G, Ciliberti A, Cotti G, Carretti D
Inst. Oncology and Tumor Center, Bologna, Italy
Environ Health Perspect; 41:3-29 1981

Bioassays of vinyl chloride (VC) monomer were performed to assess the carcinogenicity, types and locations of tumors induced, the effects of various modes of administration (particulary those simulating potential human exposure), and the level of risk. VC was administered to Sprague-Dawley rats, Wistar rats, Swiss mice, and golden hamsters. Methods of administration included inhalation (14 dose rates: 1-30,000 ppm, 4 hr/day, 5x/wk), ingestion (6 dose rates: 0.03-50 mg/kg, 5x/wk for 52 wk), ip injection (4.25 mg 1x or 2, 3, or 4x at 2-wk intervals), and sc injection (4.25 mg 1x). VC was carcinogenic in all animal systems tested and was a multipotential carcinogen, causing various types of tumors at various sites. Some tumor types occurred in all species, while some occurred only in one species. Carcinogenesis was induced by inhalation, ingestion, and possibly injection. Response was strongly affected by duration and schedule of administration and strain and sex of the animals studied. VC was carcinogenic even at low doses and produced tumors in embryos after crossing the placenta. (13 Refs)

69. OBSERVATIONS OF THE SITE-SPECIFIC CARCINOGENICITY OF VINYL CHLORIDE TO HUMANS.

Infante PF
Office Carcinogen Identification and Classification, Health Standards, Program, Occupational Safety and Health Admin. U. S. Dept. Labor, Washington, DC, 20210
Environ Health Perspect; 41:89-94 1981

Studies of site-specific carcinogenicity of vinyl chloride (VC) are reviewed. Problems encountered included relative insensitivity to carcinogenic response at low risk sites due to small sample size, and characteristics of method and design that prevent adequate interpretation of results. Restriction of disease definition resulted in obscuring some sites that might otherwise have shown significant excess risk. Four of eight studies indicated a significant risk of liver cancer following exposure to VC, although the liver had been confirmed as a site of VC-carcinogenesis by other studies. Problems with studies of liver cancer included insufficient exposure and observation times. Some studies classify liver cancer with other cancers of the digestive tract. Overall data from at least one study of cancers of the digestive tract indicate a reduction in mortality among exposed workers. An excess of mortality due to CNS cancers was indicated by five of eight studies. Some studies classified CNS cancers with nonspecific 'other' categories. Data for lung cancer mortality suggest a significant increase in risk for workers exposed to VC. Data for cancers of the lymphatic and hematopoietic systems are suggestive but not conclusive. Overall data indicates that the carcinogenic effect of VC is not limited to the liver. (12 Refs)

70. CYTOGENETIC EFFECTS OF EPOXY, PHENOLFORMALDEHYDE, AND POLYVINYLCHLORIDE RESINS IN MAN.

Suskov II, Sazonova LA
Inst. General Genetics, Acad. Sciences USSR, Moscow 117333, USSR
Mutat Res; 104(1-3):137-140 1982

Cytogenetic effects of synthetic resins were studied in workers exposed to epoxy and polyvinylchloride (PVC) in the manufacture of goods or to phenol and formaldehyde in the production of phenolformaldehyde (PF) resins. Chromosomal aberrations (CA) were analyzed in peripheral lymphocytes from resin workers (av age 39.1 yr, exposure 4 mo-30 yr) and healthy nonexposed controls. Exposure to the synthetic resins and their components was by inhalation and skin exposure. Av concentration of chemical in the air was 6 mg/cubic meter (m3) for vinyl chloride, 1 mg/m3 for epichlorohydrin (a component of epoxy resin), 0.3 mg/m^3 for phenol, and 0.5 mg/m3 for formaldehyde. Among controls CA were found in 2.4% of cells; 0.024 aberrant chromosomes (AC)/cell were found; 1.26 breaks/chromosomes were found. The frequency of CA in cells from exposed workers was 5.5% for epoxy resin, 6.1% for PVC, and 5.0% for PF. Significant increases in AC/cell were found for all compounds. A significant increase in chromosomal breaks/cell was found only for PVC. Acentric single and paired chromosomal fragments were the predominant aberration noted, accounting for 90%. Results indicate the need for further study of the hazards of occupational exposure to synthetic resins and components of the resins. (5 Refs)

71. NEEDS FOR PUBLIC HEALTH INTERVENTION AND NEEDS FOR NEW RESEARCH ON VINYL HALIDES AND THEIR POLYMERS: A PUBLIC POLICY PERSPECTIVE.

Hattis D
Center for Policy Alternatives, Massachusetts Inst. Technology, Cambridge, MA, 02139
Environ Health Perspect; 41:227-231 1981

Priorities for regulation and for research on the carcinogenic hazards of vinyl chloride (VC) and the related alkyl and vinyl halides, respiratory system hazards of poly(vinyl chloride), and reproductive hazards of VC, are discussed. The most effective use of limited resources depends on determination of the risk due to exposure under current standards and the likelihood of significant reduction in risk by revision of standards and enforcement. (8 Refs)

72. CARCINOGENIC ACTIVITY OF VINYL CHLORIDE (DATA OF CLINICO-HYGIENIC AND EPIDEMIOLOGICAL STUDY).

Filatova VS, Antoniuzhenko VA, Smulevich VB, Fedotova IV, Kryzhanovskaia NA, Bochkareva TV, Goriacheva LA, Bul'bulian MA
Res. Inst. Industrial Hygiene and Occupational Diseases, Gorky, USSR
Gig Tr Prof Zabol; (1):28-31 1982

Incidence of malignant tumors was studied in workers who had an occupational exposure to vinyl chloride (VC) and polyvinyl chloride (PVC). Group 1 was exposed to VC at greater than 300 mg/cubic meter (m3), Group 2 was exposed to VC in concentrations of 30-300 mg/m3, and Group 3 was exposed to VC in concentrations of less than 30 mg/m3. Analysis of cancer morbidity showed that 31.7% had stomach cancer, 26.9% had lung cancer and 14.3% had lymphatic and hematological malignancies. Cancer mortality index in Groups 1, 2, and 3 was 1.4, 1.3, and 0.6, respectively. Cancer mortality depended upon the duration of exposure. (15 Refs) (In RUS)

73. MUTAGENICITY STUDIES OF VINYL CHLORIDE.

Fabricant JD, Legator MS
Dept. Preventive Medicine and Community Health, Div. Environmental, Toxicology Univ. Texas Medical Branch, Galveston, TX, 77550
Environ Health Perspect; 41:189-193 1981

Studies of the mutagenicity of vinyl chloride (VC) in man and test organisms are reviewed. In vitro studies have demonstrated mutagenicity in both prokaryotic and eukaryotic organisms. In vivo studies of cytogenetic effects in animals and humans have demonstrated somatic and germinal mutations. VC hazards and the consequences of mutations are discussed. (26 Refs)

74. EFFECTS OF AGING ON THE INDUCTION OF ANGIOSARCOMA.

Groth DH, Coate WB, Ulland BM, Hornung RW
Div. Biomedical and Behavioral Science, Natl. Inst. Occupational Safety and Health
Environ Health Perspect; 41:53-57 1981

The effects of aging on chemical induction of angiosarcoma were studied in adult Sprague-Dawley albino rats. In each of four age groups (6, 18, 32, and 52 wk old at the start of exposure), 110-128 male rats and an equal number of female rats were exposed to vinyl chloride (VC: 948 ppm, 7 hr/day, 5 days/wk for a mean duration of 24.5 wk). Equal numbers of controls were kept under identical conditions but were not exposed to VC. Rats exposed to VC did not show any significant differences in mean hematological or clinical chemistry measurements at interim sacrifice times when compared with controls. Angiosarcomas were found in 28/370 exposed males and 50/387 exposed females; among controls only one sc angiosarcoma was found. Angiosarcomas occurred more frequently with increasing age at the start of exposure. Among male rats killed at unscheduled times, the occurrence rates were 0% for 6-wk-, 0% for 17-wk-, 6.7% for 32-wk-, and 24% for 52-wk-old rats. The corresponding rates for female rats were 5.3%, 15%, 47%, and 20%. Times between start of exposure and first appearance of tumors were shorter in older rats than in younger rats. Most of the angiosarcomas in exposed rat were highly anaplastic primary tumors of the liver with pulmonary metastases. Results indicate that older rats and female rats are more susceptible to induction of angiosarcomas by VC than younger rats and female rats, respectively. (3 Refs)

75. LIGHT-INDUCED GENETIC TOXICITY OF THIMEROSAL AND BENZALKONIUM CHLORIDE IN COMMERCIAL CONTACT LENS SOLUTIONS.

Lovely TJ, Levin DE, Klekowski E
Univ. Pennsylvania, Sch. Medicine, Philadelphia, PA, 19104
Mutat Res; 101(1):11-18 1982

Genetic activity of 13 commercial contact lens soln and their 3 preservatives were investigated in both the Ames Salmonella assay and the Rosenkranz Escherichia coli DNA polymerase A- assay. None of the commercial products were mutagenic for any of the Salmonella tester strains. In the E coli assay, five products were genotoxic in the dark and their activity was enhanced by illumination. All four products containing thimerosal were active while only one containing benzalkonium chloride was genotoxic. In parallel experiments, irradiation of these compounds with visible light enhanced the genotoxicity of benzalkonium chloride and induced the genotoxicity of thimerosal. (17 Refs)

76. GENOTOXIC ACTIVITY OF FIVE ANTIDEPRESSANT HYDRAZINES IN A BATTERY OF IN VIVO AND IN VITRO SHORT TERM TESTS.

Brambilla G, Cavanna M, Faggin P, Pino A, Robbiano L, Bennicelli C, Zanacchi P, Camoirano A, De Flora S
Inst. Pharmacology, Univ. Genoa, Viale Benedetto XV, 2, I-16132 Genoa, Italy
J Toxicol Environ Health; 9(2):287-303 1982

The mutagenic and potential carcinogenic activity of iproniazid (IPZ), phenelzine (PHZ), nialamide (NLM), isocarboxazid (ICB), and mebanazine (MBZ) was assessed. Mouse liver and lung DNA damage was analyzed by the alkaline elution technique after single or daily, ip or po doses of each drug, ranging from 0.333 to 2x the LD50. ICB, NLM, PHZ, and MBZ caused significant DNA fragmentation with decreasing efficiency, while IPZ was ineffective. In contrast to ICB, NLM, and PHZ, MBZ induced DNA damage only in the lung and only after five successive daily doses. Sister chromatid exchange (SCE) in mouse bone marrow cells was assessed after ip administration of 1-2x the LD50 of each drug except MBZ. SCE frequencies in the IPZ, NLM, ISB, and PHZ treated groups increased 71%, 49%, 46%, and 34%, respectively, when compared with control groups. A dose-dependent increase in SCE frequency was observed in mice treated with ICB at LD50 and 2x LD50. Mutagenic activity was investigated with the Salmonella/microsome test. NLM and PHZ were mutagenic in the spot test (1 mg/plate) and the plate incorporation test (PIT). ICB and IPZ were not mutagenic, and MBZ was weakly mutagenic in the PIT. Antibacterial activity in repair deficient Escherichia coli was also assessed for each compound. ICB and IPZ were scarcely toxic, while NLM, PHZ, and MBZ showed significantly increased antibacterial activity in some E coli strains with spot and spiral tests. Long term carcinogenic tests should be performed for NLM and ICB, which are still in clinical use. (30 Refs)

77. CYTOGENETIC ACTIVITIES OF 3 SULPHONAMIDES.

Badr A
Botany Dept., Faculty Science, Tanta Univ., Tanta, Egypt
Mutat Res; 104(1-3):95-100 1982

Cytogenetic effects of three sulfonamides were tested in Allium cepa (cv Giza). Bulbs with growing root tips were exposed to sulfadiazine (2-p-aminobenzene sulfonamide pyrimidine), sulfadimidine (2-p-aminobenzene sulfonamide 5-p-aminomethyl pyrimidine), or sulfaphenazole (5-p-aminobenzene sulfonamide-1-phenyl pyrazole) at concentrations of 0.02, 0.2, 1.0, or 2.0 mg/ml for 4, 24, or 48 hr. Cytological effects were studied by means of the Feulgen squash technique. Compared with controls, mitotic indices (MI) were increased by all three test compounds after 4-hr exposures and reduced after 24-and 48-hr exposures. Reduction in MI were concentration-dependent. Increasing exposure time from 24 to 48 hr produced only slight additional reduction in MI. MI were reduced to less than 50% of control values by concentrations of 1 or 2 mg/ml. All three test compounds produced high frequencies of mitotic and chromosomal abnormalities (C-metaphases, multipolar mitoses, polyploidy, chromosome lagging, stickiness, bridges, and breakage) after 4-hr exposures. The frequency of abnormalities was decreased after 24-hr exposures and increased relative to 24-hr exposures by 48-hr exposures. Wide variations were observed among roots undergoing the same treatment. Mitotic abnormalities were more common after 4-hr exposures, while chromosomal abnormalities were more common after 24-or 48-hr exposures. Results suggest possible mutagenic effects in humans. (18 Refs)

78. THE INFLUENCE OF ANESTHETICS ON METASTASIZING PROCESS OF EXPERIMENTALLY INDUCED TUMORS, PART I.

Stanculescu M, Popp I, Terbea I, Constantinescu M, Nutu D
Institutul oncologic, Bucharest, Romania
Rev Chir [Oncol]; 20(2):95-104 1981

The influence of certain soluble anesthetics (pentothal) on the rate of metastasizing in male rats with grafted H10 tumors was investigated. Anesthesia did not influence the development of the primary tumors, while increasing, but not significantly, the proportion of distal metastases and increasing metastatic dissemination in animals treated surgically. The preliminary nature of these results is stressed. (19 Refs) (In RUM)

79. THE EFFECT OF BLEOMYCIN ON DNA SYNTHESIS IN ATAXIA TELANGIECTASIA LYMPHOID CELLS.

Cohen MM, Simpson SJ
Div. Genetics, Children's Memorial Hosp., 2300 Children's Plaza, Chicago, IL, 60614
Environ Mutagen; 4(1):27-36 1982

The effect of bleomycin (BLM) on DNA synthesis was determined in (methyl-3H)thymidine-labeled lymphoid cells from five patients with ataxia telangiectasia (AT) and three patients with xeroderma pigmentosum (XP) compared to those from four normal subjects. BLM (5, 10, 25 and 50 ug/ml) treatment of AT cells over a period of 4 hr led to some inhibition of incorporation compared to normal cells. DNA synthesis of AT cells determined at hourly intervals after exposure to BLM (1, 5, 10, and 25 ug/ml) showed that AT cells did not attain normal levels during the 24-hr observation period whereas normal cells recovered within 15-18 hr. These differences were not found after exposure of the cells to mitomycin C. Following BLM treatment and preincubation with hydroxyurea, residual DNA synthesis was similar in AT, XP and normal lymphoid cells, suggesting that the capacity to repair the induced DNA lesion is present. (30 Refs)

80. ANTIPROTOZOAL DRUGS (SIDE EFFECTS).

Nir I
Dept. Pharmacology and Experimental Therapeutics, The Hebrew Univ., Hadassah Medical Sch., Jerusalem, Israel
Side Eff Drugs Annu; (5):278-284 1981

Side effects of antiprotozoal drugs are reviewed. Antimalarial drugs including chloroquine and hydroxychloroquine, primaquine, diformyl diaminodiphenylsulfone, pyrimethamine, and quinine are discussed; chloroquine and hydroxychloroquine are discussed with respect to ocular toxicity, neuropathy and myopathy, ototoxicity, cardiac arrest, immunoblastic lymphadenopathy, interaction, and acute intoxication. Drugs used in the treatment of other protozoal infections are examined, including metronidazole and related compounds (pseudomembranous colitis, encephalopathy, blood dyscrasias, carcinogenicity, mutagenicity, and teratogenicity), benznidazole, miconazole, secnidazole, tinidazole, emetine, hycanthone, mepacrine, oxamniquine, and pentamidine. (49 Refs)

81. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO MAN. SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.

Schmahl D
International Agency for Cancer Research, Lyon, France
IARC Mongr Eval Carcinog Risk Chem Hum 26: 411 pp., 1981.

The carcinogenic risk to humans of some antineoplastic and immunosuppressive agents is reviewed and analyzed and areas in which additional research is needed. The compounds considered, include alkylating agents, antimetabolites, mitotic inhibitors, and/or immunosuppressants. Alkylating agents are generally carcinogenic and mutagenic and produced tumors at multiple organ sites. For most drugs, only case reports were available for study. Whenever possible, concern about late complications was considered. Monographs are presented on 5-azacytidine, azathioprine, bischloroethyl nitrosourea, bleomycins, chlorambucil, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, cisplatin, cyclophosphamide, dacarbazine, 5-fluorouracil, isophosphamide, 6-mercaptopurine, methotrexate, prednisone, procarbazine hydrochloride, treosulphan, vinblastine sulfate, and vincristine sulfate. (1545 Refs)

82. CYTOSTATIC AND IMMUNOSUPPRESSIVE DRUGS (SIDE EFFECTS).

Wierzba K, Danysz A, Hamid MR
Dept. Pharmacology, Inst. for Drug Control and Res., Ul. Chelmska 30/34, 00-725 Warsaw, Poland
Side Eff Drug Annu; (5):407-418 1981

Side effects of cytostatic and immunosuppressive drugs are reviewed. Cardiotoxicity (adriamycin, rubidazone, quelamycin, 5-fluorouracil, cyclophosphamide), pulmonary toxicity (antibiotics, alkylating agents, antimetabolites), nephrotoxicity and other urinary complications (cis-dichlorodiammine-platinum, gallium nitrate, cyclophosphamide, semustine, 5-azacytidine), hepatotoxicity (methotrexate, dacarbazine), carcinogenicity, pregnancy following cytostatic therapy, and new and unusual side effects are discussed. (89 Refs)

83. TOXICITY, INTERSTRAND CROSS-LINKS AND DNA FRAGMENTATION INDUCED BY ACTIVATED' CYCLOPHOSPHAMIDE IN YEAST: COMPARATIVE STUDIES ON 4-HYDROXYPEROXY-CYCLOPHOSPHAMIDE, ITS MONOFUNCTIONAL ANALOGON, ACROLEIN, PHOSPHORAMIDE MUSTARD, AND NOR-NITROGEN MUSTARD.

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Chem Biol Interact; 39(1):1-15 1982

Activated cyclophosphamide (CP) is known to achieve its cytotoxic and alkylating capacity upon spontaneous hydrolytic breakdown of the oxazaphosphorine ring structure. Treatment of yeast cells with the chemically activated form of CP (4-hydroperoxy-CP, 4-OOH-CP) and with several potentially toxic cleavage products revealed that cytotoxicity is closely linked to the formation of DNA interstrand cross-links and to DNA fragmentation. While this holds true for 4-OOH-CP and its bifunctional alkylating breakdown products, phosphoramide mustard (PM) and nor-nitrogen mustard (NNM), equimolar concentrations of acrolein and the monofunctional analogon of activated CP were inactive. NNM, the ultimate cleavage product within the successive degradation of the oxazaphosphorine structure was 5x more toxic than 4-OOH-CP, whereas the cytotoxic action of PM was only slightly enhanced. The high cytotoxicity of NNM was matched by its ability to induce DNA interstrand cross-links: at concentrations and treatment times producing equal cell killing, 4-OOH-CP and NNM produced the same extent of cross-linking and DNA fragmentation. Biochemical potency of NNM is in contrast to data found with the NBP colorimetric assay which suggest that NNM loses its alkylating activity at neutral pH. 4-OOH-CP and PM are much more stable than predicted from half-life measurements performed via the NBP colorimetric assay: they retain a considerable fraction of their cytotoxic and cross-linking activity in spite of a 12-hr preincubation at pH 7 and 36 C. (Author abstract) (24 Refs)

84. EXPRESSION OF GENETIC DAMAGE INDUCED BY ALKYLATING AGENTS IN GERM CELLS OF FEMALE MICE.

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Mutat Res; 92(1/2):447-464 1982

The effects of trenimon (TR: 0.25 or 1 mg/kg, ip) and cyclophosphamide (CP: 150 mg/kg, ip) on germ cells were studied in female random-bred NMRI mice (10-13 wk old). Pre-ovulatory treatment with CP or the higher dose of TR caused an increase (significant with TR, slight with CP) in frequency of meiotic non-disjunction in the unfertilized oocytes but did not cause structural aberrations in second-metaphase oocytes. In mice treated with CP or the lower dose of TR before ovulation and mated with random-bred NMRI males up to 0.5 day after treatment, TR showed a strong clastogenic effect on the first-cleavage embryos (first-cleavage metaphase). Numerical and structural chromosome aberrations were observed in 63.39% of the embryos; most of the aberrations were structural aberrations of the chromatid types. The embryonic mortality rate was 55.17%, as measured in the dominant lethal assay. Similar treatment with CP enhanced the occurrence of dominant lethal effects to 58.94%. When the alkylating agents were given at longer times before mating (up to 23.5 days), their clastogenic and mutagenic effects declined with time. The results observed with TR support the conclusion that an intervening round of DNA replication is required for TR-induced DNA damage to be transformed into a structural aberration. (55 Refs)

85. INDUCTION OF CHROMATID BREAKAGE BY CLASTOGENS IN CELLS OF G2 PHASE.

Hsu TC, Cherry LM, Pathak S
Dept. Cell Biology, Univ. Texas M. D. Anderson Hosp. and Tumor Inst. at Houston, Houston, TX, 77030
Mutat Res; 93(1):185-193 1982

Clastogenicity of several compounds was tested in cultures of human peripheral blood cells in G2 phase. Cells were exposed simultaneously to Colcemid and actinomycin D (AMD: 2.8 uM for 15, 30, 45, or 60 min or 2.8, 1.4 or 0.28 uM for 60 min). Chromosome breakage was induced in a dose-dependent manner. The most frequent aberrations were chromatid breaks; chromatid exchanges were rare. In a modified procedure, cells were exposed to 2.8 uM AMD for 90 min, but to Colcemid for only the last 60 min. Among 100 metaphase figures 95% had chromatid breaks; the av number of breaks/cell was 3.77. Autoradiographic studies indicated that all chromatid aberrations occurred during G2 phase. Additional clastogens were tested at 100 uM concentrations (or at lower concentrations when 100 uM was too toxic). Chromatid breaks were produced by adriamycin, bleomycin, neutral red, gentian violet, and 1,4-dihydroxy-5,8- [*2-(2 hydroxymethyl)amino*]*ethylamino* -9,10-anthracenedione at 15-100x the frequency produced in controls. No increases in the frequency of chromatid breaks were produced by mitomycin C, hydroxyurea, ethidium bromide, or cytosine arabinoside. Cis-platinum II produced borderline results. N-Methyl-N'-nitrosoguanidine was mildly clastogenic in G2 phase. Results indicate that a simple protocol can be used to determine clastogenicity in G2-phase cells. (8 Refs)

86. DIFFERENTIAL SENSITIVITY OF MUNTJAC LYMPHOCYTE CHROMOSOMES TO MITOMYCIN C, BROMODEOXYURIDINE AND HYDROXYLAMINE AT DIFFERENT CELL-CYCLE STAGES.

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Cytogenetics Lab., Dept. Zoology, Banaras Hindu Univ., Varanasi-221005, India

Mutat Res; 93(1):161-174 1982

Aberrations were induced in muntjac (Muntiacus muntjak) chromosomes during different phases of the cell cycle using mitomycin C, 5-bromodeoxyuridine, and hydroxylamine hydrochloride. Sensitivity of cells during the cell cycle varied according to the mutagen used, but sites affected by each mutagen were specific and invariant at different phases. Phase-dependent sensitivity thus is apparently determined by the functional state of preferred sites for mutagenesis. (25 Refs)

87. A SEARCH FOR SOME COMMON CHARACTERISTICS OF THE EFFECTS OF CHEMICAL MUTAGENS IN DROSOPHILA.

Vogel EW, Blijleven WG, Kortselius MJ, Zijlstra JA

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Mutat Res; 92(1/2):69-87 1982

An analysis of shared general features was used to compare the actions of mutagens in Drosophila. Germ cell metabolism is the most significant factor determining the effects of promutagens in various cell stages. Only autosomal recessive lethal mutations can be used to compare stages sensitivity to a given mutation. Only a few mutagens have been tested in both sexes of Drosophila, including mitomycin C, bleomycin (BLM), and diethylstilbestrol. Females are much more sensitive than males to the mutagenic action of BLM, which causes recessive lethals and X-chromosomal aneuploidy in oocytes. The mutagenicities of some (not all) alkylating agents can be greatly modified by introducing repair-deficient mutants into the test system, but each new strain must be validated before it is tested with a wide variety of mutagens. The molecular mechanisms of the interactions of some methylating and ethylating agents with DNA are related to their genetic effects in germ cells. The relative proportions of chromosome aberrations to mutations and the ability of an agent to induce delayed mutations can be used to provide more information on the basic mechanisms of chemical mutagenesis. For at least some mutagens, a positive correlation has been discovered between the induction of chromosome aberrations in germ cells and the induction of an increased proportion of mosaic twin spots (relative to mosaic single spots) in somatic tissues. (68 Refs)

88. EFFECTS OF AMPHIDICOLIN ON REPAIR REPLICATION AND INDUCED CHROMOSOMAL ABERRATIONS IN MAMMALIAN CELLS.

van Zeeland AA, Bussmann CJ, Degrassi F, Filon AR, Van Kesteren-van Leeuwen AC, Palitti F, Natarajan AT

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Mutat Res; 92(1/2):379-392 1982

In growing cultures of normal human skin fibroblasts (HF) and HeLa cells, aphidicolin (APH: 5 ug/ml) enhanced DNA repair replication after UV exposure. In confluent HF cultures, APH inhibited UV-induced repair replication. This inhibitory effect was enhanced in the presence of hydroxyurea (HU: 10 milliM). In confluent HeLa cell cultures, APH inhibited UV-induced repair replication in the presence of HU but enhanced it in the absence of HU. In x-irradiated human peripheral blood lymphocytes (PBL), APH exposure during the G0 or G1 phase increased the occurrence of chromosome breaks and exchanges. The effects of APH on the induction of chromosomal damage in Chinese hamster ovary (CHO) cells depended on the cell cycle stage. In synchronized CHO cells, APH did not significantly affect the frequencies of chromosomal aberrations induced by exposure to x-rays during G2. In G2 cells, APH enhanced the frequencies of x-ray-induced chromatid breaks. In CHO cells exposed to UV, mitomycin C, monofunctional mitomycin C, or 4-nitroquinoline 1-oxide during G1 and exposed to APH in G2 (just before fixation), the frequencies of chromosomal aberrations were higher than in cells exposed only to UV or the alkylating agents. Despite the difficulty of making direct comparisons between the effects of APH on DNA-repair replication and the frequencies of induced chromosomal aberrations, these results indicate that cell type and cell cycle stage influence the biologic responses to APH. (18 Refs)

89. EFFECT OF PROCARBAZINE TREATMENT OF MICE ON ALPHA-GLYCEROLPHOSPHATE DEHYDROGENASE ACTIVITY AND FREQUENCY OF SELECTED ABNORMALITIES IN SPERM.

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Mutat Res; 92(1/2):249-256 1982

Male DBA/2J mice (10-12 wk old) were given one ip dose of procarbazine (PCB: 0-800 mg/kg). Levels of mitochondrial alpha-glycerol phosphate dehydrogenase (a-GPD) in the sperm and the frequencies of two specific sperm abnormalities (headlessness and PL-type disorganization of the mitochondrial assembly) were studied 4-55 days after treatment. PCB caused dose-related increases in the frequencies of sperm without active a-GPD and/or morphologically abnormal spermatozoa. The lowest dose causing the abnormalities was 200 mg/kg. Individual variations in response to each dose of PCB were observed. Since quantifiable changes in mitochondrial a-GPD activity were easily detected at 200 mg/kg of PCB, the measurement may be a useful indicator of a chemical agent's ability to reach the germinal tissue in an active and possibly mutagenic form. No abnormalities of spermatic morphology or a-GPD were observed 85 days after PCB administration. (14 Refs)

90. PROLIFERATIVE DEFECTS IN RENAL AND INTESTINAL EPITHELIUM AFTER CIS-DICHLORODIAMMINE PLATINUM (II).

Kovacs CJ, Braunschweiger PG, Schenken LL, Burholt DR

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Br J Cancer; 45(2):286-294 1982

The effects of cis-dichlorodiammine platinum II (DDP) on the intestinal mucosa and the kidney were studied after single and multiple treatments with intervals of 7-45 days. After a single treatment, the jejunal epithelium underwent a transient interruption of cell proliferation followed by a hyperplastic recovery and return to control proliferative rate on Day 7. Subsequent treatments led to suboptimal recovery for all treatment intervals. In contrast, DDP induced a six-fold increase in [3H]dT incorporation in the kidney by Day 7 which remained high until Day 21, and returned to near-control values by Day 45. After a single DDP treatment, the 'recovery potential' of kidneys, measured by the proliferative response to folic-acid stress, demonstrated suboptimal proliferative reserve compartments for up to 45 days. The distinction between acute and delayed sensitivity to subsequent drug treatment was more apparent in the DDP-treated kidney than in the intestinal epithelium. (Author abstract) (28 Refs)

91. A PROPOSED MECHANISM OF PRODUCTION OF THE AUTOIMMUNE AND LYMPHOPROLIFERATIVE SIDE-EFFECTS OF BETA-ADRENERGIC-SITE-BLOCKING DRUGS AND HYDANTOIN ANTICONVULSANTS.

Duggan MA, Court JB

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Ann Clin Res; 13(6):406-418 1981

The mechanism of pronethanol (PL) action is yet not clear. PL has a beta-blocking activity, and it is known for its carcinogenicity in mice. A review of literature suggests that both beta-blockers and hydantoin anticonvulsants cause lymphoid dysplasia, which may manifest itself as a lymphoreticular malignancy or as an autoimmune condition. In the case of each type of drug, the dysplasia may be explained in terms of disturbances of the normal interactions of cyclic AMP and Ca++ in the lymphocyte; these effects are consistent with the known pharmacological properties of the drugs. (168 Refs)

92. SEX HORMONES AND LIVER CANCER.

Williams GM

Naylor Dana Inst. for Disease Prevention, New York Medical Coll., Valhalla, NY

Lab Invest; 46(3):352-354 1982

The ability of hormones to produce tumors in endocrine-related organs of experimental animals and the phenomenon of two-stage carcinogenesis is reviewed. Liver tumor promotion, mechanisms of promotion, and the potential impact of use of estrogen-containing drugs on cancer development are discussed. The fact that human exposure to several promoters (eg phenobarbital and dichlorodiphenyl trichloroethane) does not appear to cause increased occurrence of liver neoplasms may mean that the agents were not present at high levels or for prolonged continuous exposure sufficient to impede cell-cell communication and thus promoting activity. (41 Refs)

93. TIME- AND CONCENTRATION-DEPENDENT INHIBITION OF THE CLONOGENIC GROWTH OF N-[4-(5-NITRO-2-FURYL)-2-THIAZOLY]FORMAMIDE-INDUCED MURINE BLADDER TUMOR CELL LINES BY CIS-DIAMMINEDICHLOROPLATINUM(II).

Niell HB, Wood CA, Mickey DD, Soloway MS
Hematology/Oncology Section, Univ. Tennessee Center for Health Sciences, Coleman Research Building, 956 Court St., Memphis, TN, 38163
Cancer Res; 42(3):807-811 1982

The influence of the concentration and time of exposure to cis-diamminedichloroplatinum on the inhibition of the clonogenic growth of three N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide mouse bladder tumor cell lines was evaluated in a tumor colony assay. Drug testing was performed in the murine model, and tumor cells were removed from the animals for in vitro testing. Murine drug testing revealed marked cis-diamminedichloroplatinum sensitivity of all three mouse bladder tumor lines. One-hr incubation in cis-diamminedichloroplatinum was an inadequate time of drug exposure to produce in vitro colony survival curves predictive of in vivo sensitivity to the drug. Furthermore, it was found that 6-to greater than 24-hr exposure to the drug was required to produce colony survival curves in the tumor colony assay predictive of tumor sensitivity. High drug concentrations using 1-hr drug incubation or continuous incubation in drug both produced colony survival curves predictive of tumor sensitivity. Both methods, however, would require higher products of the drug concentration multiplied by time curves than could theoretically be clinically achievable in the murine model. Until pharmacokinetic data on cis-diamminedichloroplatinum are available in this murine model, higher drug sensitivity boundaries than are presently being used for other chemotherapeutic agents will have to be utilized when testing these mouse bladder tumor cell lines for their sensitivity to cis-diamminedichloroplatinum in a tumor colony assay. (Author abstract) (20 Refs)

94. A REVIEW OF THE GENOTOXICITY OF FOOD, DRUG AND COSMETIC COLOURS AND OTHER AZO, TRIPHENYLMETHANE AND XANTHENE DYES.

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Mutat Res; 98(2):101-248 1982

Genetic hazards associated with the production and use of synthetic and natural dyes used as food additives are reviewed. Genotoxicity of structurally-related azo, triphenylmethane and xanthene dyestuffs used in drugs and cosmetics was considered. Particular attention was given aminoazobenzene and several of its derivatives with respect to carcinogenicity and mutagenicity. Activities of these dyes in short-term tests for genotoxicity are stressed; animal carcinogenicity and nonspecific toxicity is not emphasized. Dye metabolism and activities of dye metabolites are reviewed. Structural features of these dyes and their metabolites were assessed and an attempt was made to evaluate data with respect to correlations with tumor-inducing ability and to levels of environmental exposure. More than half of the dyes discussed have shown activity in at least one short-term test. Certain food colors may be active in vitro at levels comparable to those ingested daily. Natural colors, except for curcumin and riboflavin, were inactive. More data are required for all of the various dye groups, particularly for synthetic and natural non-azo compounds. Discussion of structure-activity must be tentative because of the lack of data and problems due to active sample contaminants. The presence of various substituents may be potentiating. No currently permitted food color which is inactive in short-term tests is considered a carcinogen, although some active colors require further animal testing. A human cancer hazard may exist where significant amounts of finished benzidine dye samples are handled. Such risks from exposures to other colors and the possibility of human germ-line mutation induction by dyes cannot be assessed in a meaningful manner. (365 Refs)

95. SUSPECTED CANCER-CAUSING AGENTS IN THE HOSPITAL ENVIRONMENT.

Kubinski H, Kubinski ZO, Javid M
4605 Medical Science Center, 1300 University Ave., Madison, WI, 53706
Ecotoxicol Environ Saf; 6(1):9-18 1982

Various substances in patient hospital rooms were tested for carcinogenicity in a short-term, in vitro DNA cell-binding (DCB) test. Substances tested included 24 cleaning agents, 7 cosmetics, 4 glues and other home repair articles, 4 insecticides and insect repellents, 4 first aid articles and local skin disinfectants, and 8 miscellaneous articles. Seventeen of the substances appeared able to induce neoplasia. Neoplastic potential was suggested for an upholstery cleaner, a toilet bowl cleaner, an all-purpose cleaner, and a cleaning agent with fungicidal properties; and for a spray deodorant, an anti-dandruff shampoo, a disinfectant skin cleanser, two mosquito repellents, two disinfectant sprays from first aid items, two parts of epoxy glue, and two shoe polishes. Metabolic activation was required by 9/17 positive substances. Articles such as cleaning agents, purchased in large quantities by hospitals, should be screened for potential carcinogenicity by a short-term assay performed in the laboratory of the hospital. Alternatively, proof of testing by the manufacturer should be mandatory. (20 Refs)

REVIEWS AND OTHER COMPOUNDS

96. MUTAGENICITY TESTING, IN BACTERIAL TEST SYSTEMS, OF SOME CONSTITUENTS OF TOBACCO.

Riebe M, Westphal K, Fortnagel P
Institut fur Allgemeine Botanik, Abteilung Mikrobiologie, Universitat Hamburg, Jungiusstrasse 6, 2000 Hamburg 36, W. Germany
Mutat Res; 101(1):39-43 1982

The Escherichia coli polA+/polA- assay for detection of repairable DNA alterations induced by mutagens and the Ames Salmonella typhimurium/microsome assay were used to test mutagenicity of 12 constituents of tobacco. None of the compounds were mutagenic in the Ames test. Positive results in the E coli test were found with pyrrolidine, nicotine, anatabine, myosmine, and 2,3'-dipyridyl; results for piperidine were inconclusive while nicotyrine was estimated to be an active substance in liquid assay. (9 Refs)

97. PRENATAL SUSCEPTIBILITY TO CARCINOGENESIS BY XENOBIOTIC SUBSTANCES INCLUDING VINYL CHLORIDE.

Rice JM
Perinatal Carcinogenesis Section, Lab. Comparative Carcinogenesis, NCI, Fort Detrick, Frederick, MD, 21701
Environ Health Perspect; 41:179-188 1981

Principles of transplacental carcinogenesis and prenatal susceptibility to vinyl chloride (VC) and related compounds are reviewed. Positive results of bioassay for carcinogenicity are indicated by a dose-related increase in incidence of tumors of one or more organ systems, a dose-related increase in multiplicity of tumors, or a shortening of latency periods. The largest number of carcinogens are small organic molecules, many of which share similar mechanisms of action. Most carcinogens require metabolic activation. The most common metabolic pathway for activation of carcinogens involves mixed-function oxidases. Assays of transplacental carcinogenicity must insure that exposure by other routes, such as through the mother's milk, is excluded. Studies in rats and mice have demonstrated that various compounds, including vinyl chloride (VC), are capable of transplacental carcinogenesis. Studies indicate that the nonhuman primate fetus is susceptible to carcinogens earlier in gestation than the rodent fetus, and different tissues are affected. Analogs of VC would be expected to have activities similar to VC. No evidence has been found suggesting that exposure of males to carcinogens leads to carcinogenesis in offspring of those males. (26 Refs)

98. MUTAGENICITY AND DNA-MODIFYING ACTIVITY OF 2-NITROPROPANE.

Speck WT, Meyer LW, Zeiger E, Rosenkranz HS
Dept. Pediatrics, Case Western Reserve Univ., Cleveland, OH, 44106
Mutat Res; 104(1-3):49-54 1982

DNA-modifying activity and mutagenicity of the industrial solvent 2-nitropropane and also 1-nitropropane, 1-aminopropane, and 2-aminopropane were examined. Using the Salmonella typhimurium mutagenicity assay, 2-nitropropane was shown to be mutagenic, 1-nitropropane had marginal activity, and 1- and 2-aminopropane were not mutagenic. Only 2-nitropropane showed DNA-modifying activity. The mutagenic, and presumably carcinogenic, effects of 2-nitropropane may be due in part to a direct, non-enzymic, reaction between the chemical and intracellular DNA. (10 Refs)

99. TEST-CONDITION-DEPENDENT INFLUENCE OF HARMAN AND NORHARMAN ON BENZO[A]PYRENE MUTAGENESIS IN SALMONELLA.

Riebe M, Westphal K, Keller H
Institut fur allgemeine Botanik, Abteilung Mikrobiologie, Universitat Hamburg, Jungiusstrasse 6, 2000 Hamburg 36, W. Germany
Mutat Res; 104(1-3):9-15 1982

The influence of harman and norharman on benzo[a]pyrene [BaP] mutagenicity was examined under various experimental conditions in the Ames test to elucidate contradictory reports of mutagenic, co-mutagenic, and non-mutagenic activities of the compounds. Conditions varied were the nature and amount of metabolizing system (S9) preparation, amount of co-factors, and relative proportion of test chemicals. Harman and norharman were not mutagenic using this test system. Activation by 3-methylcholanthrene-, phenobarbital-, and Aroclor 1254-induced mouse liver homogenates led to decreased mutagenicity of BaP in Salmonella typhimurium TA98 upon addition of harman or nonharman. Under conditions of activation by Aroclor 1254 induced rat liver homogenate, harman increased BaP revertants while norharman did not affect BaP mutagenicity. Using phenobarbital-induced mouse liver homogenate, varying the S9 extract amount, the amount of cofactors, or the relative proportions of test substances, within certain limits, had no effect on harman or norharman antagonism of BaP mutagenesis. While the Ames test is valuable in qualitatively determining mutagenicity/non-mutagenicity of single chemicals, different S9 extracts can yield widely varying results when assessing the possible synergistic or antagonistic effects of further chemicals. (8 Refs)

100. INFLUENCE OF EXPERIMENTAL CONDITIONS AND DNA REPAIR ABILITY ON EMS-INDUCED MUTAGENESIS AND DNA BINDING IN ESCHERICHIA COLI K12: COMPARISON WITH MAMMALIAN CELL MUTAGENESIS.

Mohn GR, Van Zeeland AA, Glickman BW
Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Leiden, The Netherlands
Mutat Res; 92(1/2):15-27 1982

The magnitude of ethyl methanesulfonate (EMS)-induced DNA binding and mutagenesis under different conditions was studied in Escherichia coli K12/343/113, several mutant sublines of this strain, and mammalian cell lines V79 and L5178Y. Under the same exposure conditions (120 min at 37 C, pH 7.2) and at different EMS concentrations (2.5-50 mM), the bacteria and mammalian cells showed similar levels of DNA alkylation (1.7 x 10(-4) -1.5 x 10(-3) ethylations/nucleotide). In stationary E coli cultures, the presence of L-arginine, D-glucose, and fetal calf serum during EMS exposure markedly enhanced the yields of EMS-induced mutations but did not affect the level of DNA alkylation. Nutrient accumulation by the cells may have enhanced their capacities for genetic fixation and/or phenotypic expression of premutational DNA changes. Because the mammalian cells were significantly more sensitive than repair-proficient E coli to the lethality of a given EMS concentration, the mammalian cells may have a larger genetic and/or physiologic target for cytotoxicity or a lesser ability to repair EMS-induced DNA damage. In bacterial mutants NALr and VALr, and in thioguanine-resistant (hypoxanthine-guanine phosphoribosyltransferase-deficient) and 5-bromo-2'-deoxyuridine-resistant (thymidine kinase-deficient) mammalian cells, low EMS concentrations (up to 7 mM) led to a linear dose-effect (mutation frequency) relationship with no evidence of a threshold. These experiments did not determine whether the very similar dose-effect relationships in E coli and the mammalian cells indicated that the same EMS-induced DNA adducts were responsible for the observed genetic effects. (20 Refs)

101. INDUCTION OF NUCLEAR ANOMALIES (MICRONUCLEI) IN THE PERIPHERAL BLOOD ERYTHROCYTES OF THE EASTERN MUDMINNOW UMBRA PYGMAEA BY ETHYL METHANESULPHONATE.

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Mutat Res; 104(1-3):147-152 1982

The suitability of a micronucleus test with fish as a convenient and rapid test for detecting genotoxic compounds in the aquatic environment was examined using the eastern mudminnow Umbra pygmaea. The test agent the direct-acting mutagen ethyl methanesulfonate (EMS) was administered in doses of 0-200 mg/liter over 3 wk or in 8-40 mg/liter over 6 wk. The incidence of nuclear anomalies in peripheral RBC of the mudminnows was determined. EMS caused damage to nuclei; in addition to characteristic micronuclear abnormalities, irregular Feulgen-positive structures and nuclear structural irregularities were observed. The effect of EMS was dose-dependent and very probably time-dependent. The results indicated that EMS, which is representative of a large class of alkylating agents and positive in a variety of genotoxicity tests, caused damage to the RBC nucleus of the fish U pygmaea. The test with fish RBC may be used as an alternative to the chromosome aberration test. (8 Refs)

102. MOLECULAR DOSIMETRY OF DNA DAMAGE CAUSED BY ALKYLATION. I. SINGLE-STRAND BREAKS INDUCED BY ETHYLATING AGENTS IN CULTURED MAMMALIAN CELLS IN RELATION TO SURVIVAL.

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Mutat Res; 92(1/2):361-377 1982

In cultured Chinese hamster cells, N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG), N -ethyl-N-nitrosourea (ENU), ethyl methanesulfonate (EMS), and diethylsulfonate (DES) differed markedly in their induction of DNA single-strand breaks (SSB) and alkali-labile sites (ALS) when the doses were compared on a molar basis (ENNG was about 1,000x more active than the other ethylating agents), but the agents were about equally effective in inducing SSB and ALS when doses of equal cytotoxicity were used. Prolonged alkali exposure greatly increased the number of SSB. DNA from untreated cells formed SSB slowly for about 10 hr; the rate then increased, remaining constant for up to 40 hr. Cells exposed to the ethylating agents showed an accelerated, dose-dependent linear generation of SSB for 10 hr, followed by a short plateau, followed by renewed SSB formation at a constant rate which was somewhat higher than the rate observed in untreated cells. The initial phase of SSB formation was attributed to phosphotriester hydrolysis; the causes of the later phase were unidentified. Zero intercepts seemed to be a measurement of the intracellular formation of apurinic sites. The kinetics of SSB induction as a function of lysis time (1 or 21 hr) were compared for ENNG and DES. A 24-hr repair period before lysis reduced the intercept phenomenon in cells exposed to ENNG but not DES. Since DES degraded rapidly during the 1-hr exposure period, most of the 'apurinic-site' damage was induced in the initial phases of exposure and may have been repaired at its end. The types of damage observed (reparable and nonreparable apurinic sites and phosphotriesters) seemed to be of little consequence for cell survival. (26 Refs)

103. CORRELATION OF ALKYLATING AND MUTAGENIC ACTIVITIES OF ALLYL AND ALLYLIC COMPOUNDS: STANDARD ALKYLATION TEST VS. KINETIC INVESTIGATION.

Eder E, Neudecker T, Lutz D, Henschler D
Inst. Toxicology, Univ. Wurzburg, D-8700 Wurzburg, W. Germany
Chem Biol Interact; 38(3):303-315 1982

Thirty-nine allylic and non-allylic compounds have been tested in the standard 4-(p-nitrobenzyl)pyridine (NBP) alkylating procedure and the Salmonella typhimurium mutagenicity assay. Fourteen of these were found directly mutagenic (without addition of S-9 mix activating enzyme system). With 12 of these compounds, a good correlation of alkylating and mutagenic potencies was established; the remaining 2 do not meet the chemical conditions of the NBP procedure on account of HCL elimination with these 2 compounds. The other 25 substances were inactive in both systems. The quantitative correlation proved to be almost linear in the lower activity ranges (E approx 2; revertants/umol approx 600). The reasons for some deviations from the linear relationship have been analyzed and discussed on the basis of structural features. In addition to the standard alkylation test, a modified NBP-test was performed in order to obtain kinetic data and activation energy values. The results with six representative allylic compounds show that the overall correlation is not substantially improved above that of the standard procedure; nonetheless, additional information on reaction characteristics is obtained with some substances. (Author abstract) (26 Refs)

104. REASSOCIATION OF HUMAN LYMPHOBLASTOID CELL DNA REPAIR REPLICATED FOLLOWING METHYL METHANESULFONATE TREATMENT.

Meltz ML, Whittam NJ, Thornburg WH
Dept. Radiology, Univ. Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX, 78284
Chem Biol Interact; 39(1):77-88 1982

The reassociation rates of repair replicated DNA of two human lymphoblastoid cell lines, the WIL2-A3 'normal' line and the RAJI line of Burkitt's lymphoma, were examined using the DNA/DNA 'C0t' hybridization technique. The cells were treated with methyl methanesulfonate (MMS), an alkylating agent and mutagen, to induce the repair. The incorporated repair replication radioactivity in highly repetitive sequences of WIL2-A3 cell DNA reassociates as expected for a randomly distributed incorporation. The reassociation of repair radioactivity in sequences of fewer numbers of copies, however, is less than expected for a random distribution. It is less than that occurring for semiconservatively synthesized DNA of WIL2-A3 cells co-incubated with the repair labeled DNA as an internal control. The observed difference could be due to an over-representation of repair replication radioactivity in DNA sequences with fewer copies. It is unlikely to be due to residual alkali labile damage resulting from MMS treatment, since a similar difference was not observed when semiconservatively labeled DNA from cells which had been treated with MMS for the same time and at the same concentration as in the repair experiments was substituted for repair replicated DNA in the reassociation reactions. Other possible causes of the apparent difference in the reassociation rates observed are discussed. (Author abstract) (17 Refs)

105. FORMATION OF CHROMOSOME-TYPE ABERRATIONS AT THE FIRST CLEAVAGE AFTER MMS TREATMENT IN LATE SPERMATIDS OF MICE.

Tanaka N, Katoh M, Iwahara S
Lab. Genetics, Hatano Res. Inst., Food and Drug Safety Center, 729-5 Ochiai, Hadano, Kanagawa 257, Japan
Cytogenet Cell Genet; 31(3):145-152 1981

Male mice were treated with graded dose of methyl methanesulfonate (MMS) and mated with untreated female mice during the 6 to 10 days after treatment. The nature of the primary lesions induced in late spermatids was investigated by analyzing the types and rates of chromosome aberrations in the first cleavage metaphases. The chromosome aberrations recovered at the first cleavage were predominantly of the chromosome-type. Their frequency increased exponentially with increasing dose of MMS. The results suggest that the nonenzymatic conversion of DNA containing alkylated bases to new damage, possibly strand breaks, during the maturation and storage of sperm was primarily responsible for the enhancement of the frequency of chromosome-type aberrations. (Author abstract) (28 Refs)

106. DIFFERENCES IN TEMPORAL ASPECTS OF MUTAGENESIS AND CYTOTOXICITY IN CHINESE HAMSTER CELLS TREATED WITH METHYLATING AGENTS AND THYMIDINE.

Peterson AR, Peterson H
Cancer Center, Dept. Microbiology, Univ. Southern California, Cancer Res. Lab., 1303 N. Mission Road, Los Angeles, CA, 90033
Proc Natl Acad Sci USA; 79(5):1643-1647 1982

Equitoxic concentrations of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and methyl methanesulfonate (MeMes) produced different frequencies of 5-azaguanine-resistant mutants and different amounts of N7-methylguanine, O6-methylguanine (m6G), and N3-methyladenine in the DNA of V79 Chinese hamster cells. Thus, neither the cytotoxicities nor the mutagenicities of these methylating agents could be attributed solely to nitrogen or to oxygen methylations in the DNA. However, MNNG produced 12-fold more m6G and 5-fold more mutants than did MeMes, indicating that a substantial part of the MNNG-induced mutations resulted from m6G-thymine mispairing during DNA replication. The expression as mutants of mutagenic oxygen methylations in the DNA of cells treated with MNNG was enhanced by thymidine (dThd) and deoxycytidine (dCyd), but these nucleosides did not significantly enhance MeMes-induced mutagenesis. The cytotoxicities of MNNG and MeMes were also increased by 10 uM dThd in proportion to the amount of m6G in the DNA. These increases in cytotoxicity were abolished by dCyd, which did not greatly reduce the dThd-induced enhancements of mutagenesis. Moreover, when dThd was present only during the 2-hr treatment with MNNG, maximal cytotoxicity occurred, but MNNG-induced mutagenesis was not increased. Maximal mutagenesis occurred when the dThd was present throughout the first doubling time of the MNNG-treated cells. Thus, the expression of the cytotoxicity and the mutagenicity associated with m6G in the DNA of V79 cells occurred by quite different mechanisms. (Author abstract) (31 Refs)

107. GENETIC DAMAGE CAUSED BY METHYLAZOXYMETHANOL ACETATE, THE AGLYCONE OF CYCASIN. ANALYSIS OF SISTER-CHROMATID EXCHANGE FREQUENCY UNDER IN VIVO CONDITIONS AND IN CELL CULTURES.

Gloser H
Inst. Cancer Res., Univ. Vienna, Borschkegasse 8a, A-109 Vienna, Austria
Oncology; 39(2):101-103 1982

To extend the information on the mutagenic effect of methylazoxymethanol (MAM) acetate, which has been established as a potent carcinogen, the frequency of sister-chromatid exchange (SCE) was determined in bone marrow cells of Sprague Dawley rats and in cultured rat lymphocytes. To get differentially stained chromatids under in vivo conditions, the rats received 5-bromodeoxyuridine adsorbed on activated charcoal intraperitoneally. Chromosomes were stained with fluorescence plus Giemsa. In this study a significant increase of SCE frequency after the application of various concentrations of MAM acetate could be observed both in vivo and in vitro. (Author abstract) (20 Refs)

108. METABOLISM OF BIS(2-CHLOROETHYL)ETHER AND BIS(2-CHLOROISOPROPYL)ETHER IN THE RAT.

Lingg RD, Kaylor WH, Pyle SM, Domino MM
U.S. Environmental Protection Agency, 26 W. St. Clair St., Cincinnati, OH, 45268
Arch Environ Contam Toxicol; 11(2):173-183 1982

Adult male CD-1 Sprague Dawley rats in individual cages were given a single po dose of bis(2-chloroethyl)ether (BCEE: 40 mg/kg) or bis(2-chloroisopropyl)ether (BCIE: 90 mg/kg). Both compounds contained a portion of 1-14C-labeled compound. Urine, feces, and expired air samples were taken for 48 hr, then the animals were sacrificed. Half of the radioactivity was eliminated in the urine and expired air in 12 hr for BCEE, and in 19 hr for BCIE, with relatively more of the BCIE in expired air. At 48 hr 81% of the BCEE radioactivity was recovered, 65% in urine, 11.5% in expired air, 2+% in feces, 2+% in organs and tissues, and less than 0.5% in cage wash; the corresponding figures (%) for BCIE were 73+, 47.5, 20+, 4, 2, and less than 0.5. Recovered percentages at 48 hr in blood, kidney, liver, and muscle were (BCEE and BCIE, respectively) 0.49 and 0.36, 0.56 and 0.10, 0.19 and 0.55, 0.96 and 0.50. No other localized concentrations exceeded 0.05%. Identified urinary metabolites (IUC) of BCEE consisted mostly of thiodiglycolic acid, with lesser amounts of 2-chloroethoxyacetic acid and N-acetyl-S-[2-(2-chloroethoxy)ethyl]-L-cysteine. IUC of BCIE were mainly 2-(2-chloro-1-methylethoxy)propanoic acid, half as much N-acetyl-S-(2-hydroxypropyl)-L-cysteine, and a second cysteine conjugate. Likely intermediate metabolites are discussed with regard to potential and known carcinogenicity and mutagenicity. (23 Refs)

109. INTERVENTIONAL RADIOLOGY POLYMER UPDATE: ACRYLIC.

Pevsner PH, George ED, Doppman JL, Heinz ER
(c/o George) Neurosurgery Service, Walter Reed Army Medical Center, Washington, DC, 20012
Neurosurgery; 10(3):314-316 1982

The physicochemical and biological characteristics of polyvinyl alcohol (PVA) and the monomer isobutyl 2-cyanoacrylate (IBCA), used for interventional radiology, are reviewed. While many of the physical properties of PVA make it an attractive choice for particulate embolization, early animal studies demonstrated carcinogenicity in rats. A cautious approach with PVA utilization in humans is recommended. IBCA is not a known carcinogen. It has been used surgically for greater than 15 yr and intravascularly for greater than 5 yr. Tissue response to IBCA appears to be inflammatory rather than neoplastic. Therapeutic goals of each case are used to determine which technique and materials to use; single fistula and complex angioma must be distinguished. Angiomas can be effectively treated only by total occlusion of arteriovenous communications at the tissue level. Angiomas require a liquid polymer. Gradual tissue resorption of IBCA has been observed in animal and human studies. Various polymer retardants such as ethyl 10(-iodophenyl)undecanoate or Pantopaque may be used with IBCA. The compound remains in soln in IBCA and has a pH of 6.0. The rate can be controlled in stoichiometric mixtures, achieving polymerization in 1-30 sec. However, Pantopaque is highly viscous and causes artifacts on computed tomography (CT). The viscosity problem can be solved by using octa- or decanoic acid, mild alkyl acids, or a monoalkyl phosphoric acid ester soln in IBCA. Titanium oxide produces less CT artifact than Pantopaque; however, because of particle size, the powder must be suspended in a dispersal agent. Use of hexamethyl-di-silazane for this purpose is suggested. (36 Refs)

110. PROCESS-DEPENDENT RISK OF DELAYED HEALTH EFFECTS FOR WELDERS.

Stern RM
Danish Welding Inst., 2600 Glostrup, Denmark
Environ Health Perspect; 41:235-253 1981

Estimation of process-dependent risks for delayed health effects in welders is discussed. Welding is a widely used technology which employs a wide variety of processes and materials. Welding itself creates high local concentrations of fumes containing a large number of biologically active chemicals of varying toxicity. Content of the fumes depends on the specific materials used and other factors such as welding voltage. Exposure varies considerably depending on job situation. Chemical components of welding fumes include aluminum oxide, nitrogen dioxide, chromium (VI), copper, ozone, and molybdenum. In vitro and in vivo studies of representative welding fumes have demonstrated mutagenic, embryotoxic, cytotoxic, and genotoxic effects. Epidemiological studies indicate that welders may have increased risk of pneumoconiosis, siderosis, pulmonary fibrosis, and cancer. Wide variations in exposure and other factors necessitate the establishment of standard protocols in future research. For control of working conditions, emphasis on identifying occupational 'hot spots' where exposure is greatest is recommended. (94 Refs)

111. THE ETIOLOGY, EPIDEMIOLOGY, AND PREVENTION OF LUNG CANCER.

Wynder EL
American Health Foundation, 320 East 43rd St. New York, NY, 10017
Semin Respir Med; 3(3):135-139 1982

The risk of lung cancer increases proportionally with the number of cigarettes smoked/day and the number of yr smoked. Smoking is the primary cause of lung cancer. Epidemiologic studies have suggested that risk of lung cancer decreases with reductions in the amount of tar in cigarettes smoked. Occupational exposure to asbestos, uranium, arsenic, coal products, bischloromethyl ether, vinyl chloride, nickel, chromium, iron oxide, and mustard gas is also associated with an increased risk of lung cancer. Some occupational exposures work synergistically with tobacco smoke. The higher rate of lung cancer in cities than rural areas can be explained by higher frequency of smoking, more occupational exposure to carcinogens, and higher reporting of lung cancer. The relationship between passive inhalation of cigarette smoke and lung cancer is unproven. Lung cancer can be prevented by preventing smoking in children, the cessation of smoking by adults, and by developing less harmful cigarettes. (15 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

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Section Clinical Oncology, Dept. Veterinary Surgery, Univ. California, Davis, CA, 95616

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HYDRAZINES AND RELATED COMPOUNDS

1. SURGICAL RESECTION OF THE RAT COLON: EFFECTS ON CARCINOGENESIS BY 1,2-DIMETHYLHYDRAZINE.

Rubio CA, Nylander G
Dept. Pathology, Karolinska Sjukhuset, Box 60500, Stockholm, Sweden S-104 01
JNCI; 68(5):813-815 1982

Following a 3-month treatment with 1,2-dimethylhydrazine (DMH) given weekly (sc), outbred Sprague-Dawley rats were

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subjected to partial resection of the transverse colon. After surgery, DMH treatment was continued for 6 months, after which the rats were killed. At autopsy, 63% of the tumors were found in the transverse colon. By contrast, only 29% of the tumors found in the 'sham-operated' control animals occurred in the transverse colon. Surgical trauma in the colon mucosa subjected to the action of carcinogenic agents appeared to promote the conditions suitable for the development of tumors in that organ. (Author abstract) (16 Refs)

2. BILE ACIDS: EFFECTS ON ABSORPTION OF 1,2-DIMETHYLHYDRAZINE AND 7,12-DIMETHYLBENZ[A]ANTHRACENE IN THE COLON OF THE RAT AND GUINEA PIG.

Rose RC, Nahrwold DL

Dept. Surgery, Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA, 17033

JNCI; 68(4):619-622 1982

The specific effects of bile acids as cocarcinogens were investigated. Absorptions of [14C]7,12-dimethylbenz[a]anthracene, [14C]dimethylhydrazine ([14C]DMH), and [3H]inulin from loops of colons from outbred Sprague-Dawley rats and Hartley guinea pigs were determined. In each animal absorption of one carcinogen and inulin was studied in one control loop and in a experimental loop containing either deoxycholic acid (DOC) or chenodeoxycholic acid (CDOC). DOC had a more pronounced effect on increasing loss of carcinogen from the intestinal lumen than did CDOC. This role of bile acids was consistent with their known effect of increasing intestinal permeability. Less carcinogen remained in the colon mucosa when DOC was present in the intestinal lumen. Although [14C]DMH was absorbed more rapidly from the intestinal lumina of guinea pigs than from those of rats, the rat accumulated more of the carcinogen in the intestinal mucosa and liver. (Author abstract) (16 Refs)

3. PH-SENSITIVE MUTAGENIC ACTIVITY OF OZONE-TREATED 1,2-DIMETHYLHYDRAZINE IN THE SALMONELLA/MICROSOME ASSAY.

Chambers TM, Burleson GR

(c/o Burleson) Lobund Lab., Dept. Microbiology, Univ. Notre Dame, Notre Dame, IN, 46556

Mutat Res; 94(1):23-29 1982

It has been previously shown that ozonation of 1,2-dimethylhydrazine (DMH) converts this normally inactive compound into a chemical species capable of inducing revertants in the Ames Salmonella typhimurium/microsome assay. It is shown that the mutagenicity of this ozonation-induced product is pH-dependent. The product of ozonation in basic solution was not mutagenic, while the product of ozonation in acidic solution was highly mutagenic. The mutagenic product was inactivated by raising the pH. Mutagenicity of ozonated DMH was detected at concentrations as low as 30 ug/ml at pH 2.5, and 60 ug/ml at pH 7. Toxicity to TA1535 was observed at pH 2.5 at concentrations greater than 600 ug/ml, while DMH ozonated at pH 7 was not toxic at concentrations as great as 3 mg/ml. Spontaneous reversion frequency was not affected by sample pH. These results suggest that ozonation produces a mutagen that is stable in acid but is labile at high pH. That hydrazines may be an exception to the phenomenon of inactivation of chemical carcinogens by ozonation is discussed in light of the use of ozonation in waste water treatment. (20 Refs)

HETEROCYCLIC COMPOUNDS

4. MUTAGENICITY OF CHLOROALKENE EPOXIDES IN BACTERIAL SYSTEMS.

Kline SA, McCoy EC, Rosenkranz HS, Van Duuren BL

Enzo Biochem, Inc., 325 Hudson St., New York, NY, 10013

Mutat Res; 101(2):115-125 1982

Epoxides of six chloro-olefins, cis-1-chloropropene oxide (1), trans-1-chloropropene oxide (2), cis-1,3-dichloropropene oxide (3), trans-1,3-dichloropropene oxide (4), trichloroethylene (5) and tetrachloroethylene oxide (6), were examined for mutagenicity in Salmonella typhimurium TA 1535 and Escherichia coli WP2 uvrA and for genotoxicity in E coli pol A-/pol A+ DNA repair assay in the absence of metabolic activation. In mutagenicity tests, the compounds (CPD) generally exhibited toxicity. However, at lower doses, concentration-dependent mutagenic responses in Salmonella TA1535 were obtained for all chemicals except for CPD 5. Similar results were obtained with E coli WP2 uvrA except that neither CPD 5 nor 6 were mutagenic. CPD 3 and 4 showed the highest specific mutagenicities. Both CPD 4 and its aqueous decomposition product exhibited dose-dependent mutagenicity, although the unhydrolyzed form was 2-3x more potent. In genotoxicity tests, CPD 1, 2, 3, and 4 were mutagenic for S typhimurium TA1535 and for E coli WP2 uvrA and differentially inhibited the E coli DNA repair-deficient strain. CPD 5 was not mutagenic for Salmonella and E coli WP2 uvrA, but exhibited DNA-modifying activity. CPD 6, while non-mutagenic for E coli WP2 uvrA, was mutagenic for Salmonella, and positive in the E coli pol A1-assay. CPD 3 and 4 exhibited the highest potencies in all the systems studied. The results indicated that alpha-chloroepoxides of biologically active halo-olefins are themselves biologically active in the absence of metabolic activation. (38 Refs)

5. SISTER CHROMATID EXCHANGES INDUCED IN RABBIT LYMPHOCYTES BY ETHYLENE OXIDE AFTER INHALATION EXPOSURE.

Yager JW, Benz RD

Dept. Biomedical and Environmental Health Sciences, Sch. Public Health, Univ. California, Berkeley, CA, 94720

Environ Mutagen; 4(2):121-134 1982

The dose-effect relation between inhalation of ethylene oxide (ETO) and potential genotoxic effects as measured by sister-chromatid exchanges (SCE) was studied in 4-mo-old New Zealand white rabbits. Animals were exposed to 0, 10, 50, and 250 ppm ETO for 6 hr/day, 5 days/wk, for 12 wk. A dose-related increase in SCEs in peripheral lymphocytes was observed at 50 and 250 ppm, but not at 10 ppm; SCE levels declined after treatment, but 4 mo later levels were still above control levels. No effects on standard hematological measurements (RBC, WBC, hematocrit, hemoglobin concentration) were observed at any ETO concentration. Liver nonprotein sulfhydryl content (total) did not differ between exposed and control animals, nor did blood glutathione levels differ between the two groups. Exposure to ETO produced a slight suppression of growth as indicated by measurement of weight. Of the several toxicological end points examined after exposure to ETO for 12 wk, SCE in peripheral lymphocytes were the most sensitive indicator of exposure. (40 Refs)

6. CARCINOGENICITY OF 2-AMINO-4-(5-NITRO-2-FURYL)THIAZOLE IN RATS BY ORAL AND SUBCUTANEOUS ADMINISTRATION.

Wang CY, Kamiryo Y, Croft WA

Dept. Chemical Carcinogenesis, Michigan Cancer Foundation, 110 E. Watten Ave., Detroit, MI, 48201

Carcinogenesis; 3(3):275-277 1982

Female Fischer rats were divided into two groups and fed either basal diet or basal diet containing 0.166% 2-amino-4-(5-nitro-2-furyl)thiazole for 52 wk followed by basal diet for an additional 16 wk. Out of the 24 rats fed 2-amino-4-(5-nitro-2-furyl)thiazole, 23 had forestomach tumors, 4 had fibroadenomas and 2 had adenocarcinomas in the mammary glands, 2 had renal pelvic carcinomas, 5 had papillomas and 6 had carcinomas in the bladder, and 2 had cutaneous tumors. None of the 10 rats fed basal diet developed tumors. In another study, 2-wk-old Fischer rats of both sexes were injected sc once a wk for the first 8 wk with 2-amino-4-(5-nitro-2-furyl)thiazole at a dose of 10 mg/kg and then 1.4 mg/rat for an additional 46 wk. The control rats were injected with solvent (dimethyl sulfoxide:water, 1:1) only. The experiment was terminated at the end of 58 wk. Malignant fibrous histiocytomas were found in 5 out of 8 male rats and 4 out of 11 female rats, and and angiosarcoma was found in one out of eight male rats injected with 2-amino-4-(5-nitro-2-furyl)thiazole. None of the control rats developed tumors. (Author abstract) (12 Refs)

7. THE ASSAY OF MICROSOMAL EPOXIDE HYDROLASE IN NORMAL AND PATHOLOGICAL HUMAN LIVER.

Craven AC, Walker CH, Murray-Lyon IM

(c/o Walker) Dept. Physiology and Biochemistry, Univ. Reading, Reading, England

Biochem Pharmacol; 31(7):1321-1324 1982

Samples of normal and pathological human liver were assayed for microsomal epoxide hydrolase activity using the chlorinated epoxide HEOM as substrate. The enzyme activity in liver samples from normal patients was 72.3 +-9.8 nmoles mg protein/min which is comparable to the highest values recorded in mammals, and much higher than those found in rats and mice. A microassay procedure was developed to enable the estimation of activity in needle biopsy samples (5-20 mg), obtained from patients with normal and diseased livers. Three epileptic patients who had received regular doses of phenobarbitone and/or phenytoin showed activities significantly higher than those found in all other samples (P less than 0.01). These appeared to be examples of enzyme induction. Assays were also performed on samples from six patients with alcohol-related liver disease and one patient with hepatocellular carcinoma. The role of epoxide hydrolase in the metabolism of carcinogenic epoxides is discussed in relation to these findings. (Author abstract) (18 Refs)

INORGANIC AGENTS AND PARTICULATES INCLUDING FIBERS

8. PHAGOCYTOSIS OF PARTICULATE NICKEL COMPOUNDS BY RAT PERITONEAL MACROPHAGES IN VITRO.

Kuehn K, Fraser CB, Sunderman FW

(c/o Sunderman), Univ. Connecticut Sch. Medicine, 263 Farmington Ave., Farmington, CT, 06032

Carcinogenesis; 3(3):321-326 1982

Phagocytic indices of 17 nickel compounds were measured in vitro in monolayer cultures of rat peritoneal macrophages. The macrophages were exposed for 1 hr at 37 C to particles (1.5 um median diameter) of the nickel compounds, at concentrations of 10 ug/ml of medium (2 ug/cm2 of monolayer). Phagocytic indices (ie, the percentages of macrophages with one or more engulfed particles) ranged from 69% (NiO) to 3% (amorphous NiS). In order of decreasing phagocytic indices, the 17 nickel compounds were ranked as follows: NiO greater than Ni4FeS4 greater than NiTiO3 greater than NiSe greater than alphaNi3S2 greater than Ni greater than Ni5As2 greater than NiS2 greater than NiFe alloy greater than NiSb greater than Ni11As8 greater than Ni3Se2 greater than betaNiS greater than NiTe greater than NiAs greater than NiAsS greater than amorphous NiS. Rank-correlation (p less than 0.03) was observed between the phagocytic indices of the nickel compounds and their dissolution half-times in rat serum. Nickel subsulfide, alphaNi3S2, was a notable exception to the general concordance between phagocytic indices and dissolution half-times: alphaNi3S2 was avidly phagocytized by macrophages, yet it had one of the shortest dissolution half-times. Preliminary results of carcinogenesis tests of 14 of the nickel compounds do not indicate significant rank-correlation between the phagocytic indices of the nickel compounds and the sarcoma incidences at 1 yr after im administration of the compounds to rats. (Author abstract) (55 Refs)

9. APPLICATION OF THE IN VITRO EMBRYO CULTURE TO THE STUDY OF THE MUTAGENIC EFFECTS OF NICKEL IN MALE GERM CELLS.

Jacquet P, Mayence A

Dept. Radiobiology, Mammalian Genetics Lab., CEN/SCK, B-2400 Mol, Belgium

Toxicol Lett; 11(1/2):193-197 1982

The effect of nickel treatment of male mice on embryo development in culture was investigated. Two groups of 10 male mice were injected ip with either 40 or 56 mg/kg of nickel nitrate and mated with superovulated females. Cleaved eggs were cultured; embryos reaching the blastocyst stage were examined for their ability to match and to implant with a well formed inner cell mass. The proportion of well formed inner cell masses to cultured blastocysts ranged from 57.31 to 72.73% in the 40 mg/kg-treated group and from 47.66 to 64.84% in the 56 mg/kg group. Control values ranged from 43.94 to 67.80% in both groups. The fertilization capacity of the spermatozoa, egg cleavage ability, ability of the embryo to transform into blastocyst, and hatching and implanting ability was not affected in the 40 mg/kg group. The proportion of uncleaved (unfertilized) eggs compared to controls was significantly higher in the 56 mg/kg group 3 and 4 wk after nickel nitrate treatment. Cleaved eggs in this group were able to reach the blastocyst stage and to form an inner cell mass. Nickel treatment reduced the fertilization capacity of the spermatozoa due to the toxic effect of nickel on the spermatid and spermatocyte populations. (12 Refs)

10. CARCINOGENESIS: PROBLEMS AND PARADOXES. THE 1981 GEORGE H. GEHRMANN LECTURE.

Kotin P

4505 South Yosemite, 339, Denver, CO, 80237

JOM; 24(4):290-294 1982

Carcinogenesis is discussed in relation to carcinogens in the workplace and their regulation. Data on carcinogens remains highly controversial; little progress has been achieved in the application of such data. Research must be evaluated in terms of protocol design and implementation, who performed it, and where it was performed. Dilemmas in answering basic questions are described, using controversies surrounding asbestos as an example. The gaps between information and knowledge and between technology and comprehension are considered. Cultural, political, and economic factors affect the way information is interpreted and may result in certain compromises regarding carcinogens. Public recognition of risk has been associated with a person's sense of control over the hazard, the appearance of the hazard as a single event or as individual events scattered over time and space, and the familiarity of the risk. Technics to determine risk are discussed. Action with regard to carcinogens should include the determination of a true estimate of the magnitude of the problem, examination of workers' compensation, review of differences between large and small companies and respective regulation, education of workers about the material they work with and why certain work practices are necessary, and education of the public. Recommendations for resolving problems surrounding carcinogens are presented. (10 Refs)

11. THE PHAGOCYTOSIS AND TRANSFORMING ACTIVITY OF CRYSTALLINE METAL SULFIDE PARTICLES ARE RELATED TO THEIR NEGATIVE SURFACE CHARGE.

Abbracchio MP, Heck JD, Costa M

(c/o Costa) Div. Toxicology, Dept. Pharmacology, Univ. Texas Medical Sch. Houston, P.O. Box 20708, Houston, TX, 77025

Carcinogenesis; 3(2):175-180 1982

Crystalline nickel sulfide (alphaNiS) and cobalt sulfide (CoS2) particles can cause greater cell transformation and cellular toxicity than the respective amorphous metal sulfide particles. Cultured mammalian cells phagocytose the crystalline metal sulfide particles more readily than the amorphous ones. In the case of the nickel sulfides, the crystalline metal sulfide particles had negatively charged surfaces (Zeta potential:-27.012 mV) in contrast to the amorphous particles, which were positively charged (Zeta potential: +9.174 mV). X-ray photoelectron spectroscopy analysis of amorphous and crystalline NiS particles revealed that the outermost surface (1-4 nm) of the two particles had striking differences in Ni/S ratios and in their sulfur oxidation states. Rendering particles' surfaces more negative by reduction with lithium aluminum hydride enhanced their phagocytosis, and in the case of amorphous NiS chemical reduction resulted in an incidence of morphological transformation of Syrian hamster embryo cells comparable to that observed with untreated crystalline alphaNiS. (Author abstract) (17 Refs)

12. BIOLOGICAL EFFECTS OF NICKEL-CONTAINING DENTAL ALLOYS.

Moffa JP

US Public Health Service Hosp., 15th Ave. and Lake St., San Francisco, CA, 94118

J Am Dent Assoc; 104(4):501-505 1982

Nickel chromium alloys have been used for 25 yr; with increasing cost of noble metal based alloys, use of base metal alloys has increased significantly, particularly within the years 1979-1980. This increased exposure has prompted retrospective studies of possible carcinogenic risk due to nickel. Carcinogenicity of nickel and nickel compounds has been implicated in epidemiologic studies of workers exposed to nickel in Wales, Canada, Norway, the Soviet Union, Japan, France, Germany and the United States. Workers associated with nickel refining, smelting or electroplating have shown the highest incidence of cancer of the respiratory organs. Studies with rats and mice produced benign and malignant tumors whether nickel subsulfide. was inhaled or injected as nickel subsulfide. Results from animal studies are equivocal. In the general population, 9% of women and 0.9% of men show a positive patch test to nickel. A study of allergic response to nickel-containing dental alloys indicated that 80% of confirmed nickel-sensitive patients also had a positive dermal response to dental nickel-chromium alloy. The current nickel exposure standard, as set by Occupational Safety and Health Administration (OSHA), is an 8 hr time-weighted average concentration of 1,000 g/cubic meter. The National Institute for Occupational Safety and Health (NIOSH) has recommended that the OSHA standard should reduce limits of airborne nickel levels by 80 times. (37 Refs)

13. CARCINOGENIC AND FIBROGENIC EFFECTS OF ZEOLITES: PRELIMINARY OBSERVATIONS.

Suzuki Y

Environmental Sciences Lab., Dept. Community Medicine, Pathology, Mount Sinai Sch. Medicine City Univ. New York, One Gustave L. Levy Place, New York, NY, 10029

Environ Res; 27(2):433-445 1982

Two natural zeolite minerals, erionite, a fibrous form, and mordenite, a mixture of fibrous and granular types, were injected intraperitoneally into 45 Swiss albino male mice with a single administration of 10 or 30 mg of zeolite suspended in 1 cc of saline solution. The erionite was 0.4-24 um in length (1 um av, 95% shorter than 8 um) and 0.01-2.5 um in width (0.1 um av, 94.4% smaller than 1 um). The granular mordenite was 0.33-5.7 um in the long axis and 0.27-1.67 um in the short axis. The fibrous mordenite was 0.4-6 um in length and 0.05-0.67 um in width. Thirteen untreated mice and five mice treated with 10 mg chrysotile (Calidria, 90% shorter than 1 um) were used as controls. Six of 10 mice treated with 10 mg of erionite developed malignant peritoneal tumors between 8 and 22 mo after the single administration. The neoplasms in four of the six animals were consistent with malignant mesothelioma. Two of four chrysotile-treated controls also developed malignant peritoneal mesotheliomas between 8 and 16 mo. A fibrogenic effect was noted in both the erionite- and mordenite-treated mice, the effect being more pronounced in the former. Fibrotic lesions induced by these mineral fibers commonly presented in the primary site of these induced peritoneal tumors. Findings suggest that the carcinogenic and fibrogenic effects of the fibrous erionite are similar to those of asbestos. (Author abstract) (19 Refs)

14. ABSENCE OF MUTAGENIC ACTIVITY OF THREE FORMS OF ASBESTOS IN LIVER EPITHELIAL CELLS.

Reiss B, Solomon S, Tong C, Levenstein M, Rosenberg SH, Williams GM
Naylor Dana Inst. Disease Prevention, American Health Foundation, 1 Dana Road, Valhalla, NY, 10595
Environ Res; 27(2):389-397 1982

The amosite, crocidolite, and chrysotile forms of UICC asbestos were assayed for their ability to induce gene mutations at the hypoxanthine-guanine phosphoribosyl transferase locus. Using adult rat liver-derived (ARL-6 and ARL-18) cells in culture, no consistent or significant increase occurred in the number of mutants resistant to the purine analog, 6-thioguanine, after exposure to toxic levels of amosite, crocidolite, or chrysotile. These results support the concept that asbestos is an epigenetic carcinogen that does not alter DNA. (Author abstract) (55 Refs)

15. CRITERIA FOR THE DIAGNOSIS OF ASBESTOSIS AND CONSIDERATIONS IN THE ATTRIBUTION OF LUNG CANCER AND MESOTHELIOMA TO ASBESTOS EXPOSURE.

McCullagh SF, Aresini G, Browne K, Korsgaard B, Lepoutre J, Lesage M, Lewinsohn HC, Mansour F, Mills MC, Paul WR, Raffaelli C, Smither WJ, Tucker RB, Murray R, Loison C
No affiliation given
Int Arch Occup Environ Health; 49(3/4):357-361 1982

Asbestosis is defined as an irreversible, diffuse fibrosis of the parenchyma of the lung due to inhalation of asbestos fibers. The criteria for diagnosis are discussed: (a) history, (b) clinical signs and symptoms, (c) radiological aspects, (d) other investigations (asbestos [ferruginous] bodies, biopsy), (e) lung function abnormalities, (f) differential diagnosis. Mesothelioma (M) attributable to asbestos has a latency of 20-40+ yr, although it need not be associated with even minimal asbestosis. Diagnosis of M should be based on necropsy, with attention given to excluding the tumor being a metastasis from another site. In industrial populations, while most M is associated with asbestos, no such association is seen in 10-30% of the cases. While smoking does not affect the likelihood of contracting M, it does increase the likelihood of asbestos workers contracting lung cancer. Except at lower levels of exposure, asbestos workers are at risk for bronchogenic cancer. There is no distinctive pathology for asbestos-induced lung cancer. In the presence of asbestosis, an adenocarcinoma situated peripherally and in a lower zone is indicative of asbestos exposure 15 or more yr previously. (no Refs)

16. FIBER COUNTING AND ANALYSIS IN THE DIAGNOSIS OF ASBESTOS-RELATED DISEASE.

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Dept. Pathology, Univ. British Columbia, 2211 Wesbrook Mall, Vancouver, British Columbia V6T 1W5, Canada
Hum Pathol; 13(4):381-392 1982

Analysis of numbers and types of asbestos fibers present in lung tissue may provide insights into the pathogenesis of asbestos-induced disease, as well as diagnostic information concerning the relationship of a given lesion to asbestos exposure. This type of analysis requires extraction of fibers and asbestos bodies from lung tissue, preferably by means of a digestion-and-concentration technique, and examination with a combination of electron optical techniques, including electron diffraction and energy-dispersive x-ray spectroscopy. The combination permits definitive identification of asbestos fibers. Asbestos bodies have been shown to contain asbestos no matter what population they are found in, but they appear to be of value in ascertaining unusual exposure only when present in very large numbers. Numbers of asbestos bodies markedly underestimate total numbers of fibers present in lung. In patients from the general population, the mean number of asbestos fibers is about 1 X 10(6)/g dry lung; of this number, more than 80% are fibers of chrysotile less than 5 um long. Patients in the general population who have pleural plaques have about the same total number of fibers, but their lungs contain about a 50-fold increase in long thin amphibole fibers of commercial origin. Patients who have asbestosis and most patients who have mesothelioma have 100 to 200 X 10(6) fibers/g dry lung; the grade of asbestosis appears to be related to total fiber content. Occasional patients may develop mesotheliomas with much smaller fiber burdens. Both benign and malignant pleural diseases appear to be closely related to the presence of long thin amphibole fibers. Analysis of pulmonary fiber burden suggests that asbestos-related disease is not merely a matter of total numbers of fibers present, but that factors such as fiber type and size are equally important. (Author abstract) (53 Refs)

17. THE INFLUENCE OF MINERAL DUSTS ON METABOLIC CO-OPERATION BETWEEN MAMMALIAN CELLS IN TISSUE CULTURE.

Chamberlain M
Environmental Safety Div., Unilever Res., Colworth House, Sharnbrook, Bedford, England
Carcinogenesis; 3(3):337-339 1982

Carcinogenic UICC amosite asbestos has been tested in V79-4 cultures to determine whether it acts like a tumor promoter, such as TPA, by inhibiting metabolic cooperation. TPA inhibited metabolic cooperation at the non-toxic dose of 0.01 ug/ml but UICC amosite did not inhibit the cell to cell communication even at a toxic dose. Min-U-Sil silica and ball-milled amosite which were included as non-carcinogenic control dusts similarly did not inhibit metabolic cooperation. (Author abstract) (35 Refs)

AMIDES, CARBAMATES AND UREAS

18. PARENTAL EXPOSURE TO X RAYS AND CHEMICALS INDUCES HERITABLE TUMOURS AND ANOMALIES IN MICE.

Nomura T
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Nature; 296(5857):575-577 1982

A summary is presented of the effects of radiation (RT) with x-rays and various chemicals in mice studied in multiple generations over a 13-yr period and involving 12,905 live-born mice and 9,645 fetuses from 2,904 parents. There was almost a linear increase in dominant lethals following radiation (RT) of spermatids, spermatozoa, and oocytes. There was no significant increase after treatment of spermatogonia. No increase in dominant lethals was produced by treatment with urethan (U). There was a large and significant increase in anomalies in progeny of parents treated with RT or U; only open eyelid, the predominant non-lethal anomaly, was shown to be transmissible. Both RT and U significantly increased the number of tumors in progeny regardless of which sex was treated. The dose-response data for RT showed a clear increase with dose for treatment of post-meiotic stages in males and less clear results for treatment of spermatogonia. Oocytes at late follicular stages were resistant to 36-108 rad of x-rays but were very sensitive to higher doses. As to site, 87% of induced tumors were in the lung with the remainder in many other sites. To confirm that the induced tumors were heritable, after initial treatment of only the male parent, the F1 progeny of treated parents were mated and their progeny examined. Besides treatment with RT and U, some mice were treated with 4-nitroquinoline 1-oxide. The induced tumors were inherited as if they were dominant mutations with about 40% penetrance. (12 Refs)

19. PARENTAL MUTAGENESIS AND FAMILIAL CANCER.

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Nature; 296(5857):488-489 1982

Comments are presented on the study of Nomura in which tumor incidence in offspring of male and female mice exposed to x-rays or urethan (U) was followed over a number of generations. In a 10-yr study with some 15,000 mice, it is noted that exposure of late-stage male or female germs cells to x-rays gives a linear increase in dominant lethals with dose, but no increase in those exposed to U. Parental exposure to both agents resulted in congenital abnormalities in F1 embryos, with a clear dose-response relationship for offspring derived from irradiated late-stage germ cells. (17 Refs)

20. HEMIN-INDEPENDENT CONTROL OF GLOBIN SYNTHESIS IN FRIEND ERYTHROLEUKEMIA CELLS INDUCED TO DIFFERENTIATE.

Stringer EA, Friend C
Mollie B. Roth Lab., Center Experimental Cell Biology, Mount Sinai Sch. Medicine, City Univ. New York, New York, NY, 10029
Proc Natl Acad Sci USA; 79(6,part1):1839-1843 1982

A hemin-independent translational inhibitor that prevents synthesis of rabbit globin when uninduced Friend leukemia (FL) cell and rabbit reticulocyte lysates are mixed cannot be detected in FL cells induced to differentiate. Mixing of lysates of FL cells induced with hexamethylene bisacetamide or aminonucleoside of puromycin and rabbit reticulocytes does not cause inhibition of rabbit globin synthesis. Induction also results in the cells acquiring sensitivity to the inhibitor from uninduced FL cells. A reduction in total protein synthesis is observed when uninduced and induced FL cells lysates are mixed. Inhibition does not result from competition by an excess of uninduced FL cell mRNA species for the translational machinery because uninduced FL cell lysates retain their inhibitory activity after treatment with micrococcal nuclease. Rabbit globin mRNA recovered from rabbit reticulocyte lysates that have been incubated with lysates of uninduced FL cells can still be translated effectively, indicating that inhibition does not result from modification of other species of mRNA by uninduced FL cell lysates. A switch to hemin-dependent translational control does not follow induction of differentiation. The rate of amino acid incorporation in induced FL cell lysates, like that in uninduced FL cell lysates, is unaffected by omission of exogenous hemin from the system. Its presence is not required to prevent activation of heme-regulated inhibitor. From these data, it is clear that the control of protein synthesis in FL cells, whether or not they are induced, is different from that regulated by hemin in normal erythroid cells. (Author abstract) (32 Refs)

21. COMPARISON OF SISTER CHROMATID EXCHANGE INDUCTION AND KNOWN CARCINOGENIC ACTIVITIES OF VINYL AND ALLYL CARBAMATES.

Cheng M, Conner MK
(c/o Conner) Dept. Industrial Environmental Health Sciences, Biostatistics, Univ. Pittsburgh, Pittsburgh, PA, 15261
Cancer Res; 42(6):2165-2167 1982

In vivo sister chromatid exchange (SCE) induction by vinyl and allyl carbamates was examined in alveolar macrophage, bone marrow, and regenerating liver cells of C57BL/6J x DBA/2J F1 mice. Allyl carbamate was effective in producing increases in SCE frequencies (relative to base-line SCE) over a dose range of 220 umol/kg (approx 2x base line) to 2.2 mmol/kg (3x base line). In general, alveolar macrophage and regenerating liver cells had higher responses, although not significantly, than did bone marrow. Vinyl carbamate produced significant increases in SCE frequencies over a dose range of 10 umol/kg (2x base line) to 75 umol/kg (8 to 10x base line). At the highest dose, SCE frequencies in extrahepatic tissues of hepatectomized mice were significantly higher than in intact mice and, within hepatectomized mice, alveolar macrophage and regenerating liver cell responses were greater than were bone marrow responses. Vinyl carbamate was approx 30x as potent a SCE inducer than we reported previously for ethyl carbamate. To date, our studies of six different carbamate esters have indicated a striking similarity in relative potencies for SCE induction and their known tumorigenic potencies. (Author abstract) (11 Refs)

22. INDUCTION OF SISTER-CHROMATID EXCHANGES BY INDIRECT MUTAGENS/CARCINOGENS IN CULTURED RAT HEPATOMA AND ESOPHAGEAL TUMOR CELLS AND IN CHINESE HAMSTER DON CELLS CO-CULTIVATED WITH RAT CELLS.

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Mutat Res; 93(2):409-418 1982

The inducibility of sister-chromatid exchanges (SCEs) in rat ascites hepatoma (AH66-B) and a rat esophageal tumor (R1) cell lines by 2-acetylaminofluorene, butylbutanolnitrosamine, cyclophosphamide, urethane, 4-aminoazobenzene, 2-methyl-4-dimethylaminoazobenzene, 3'-methyl-4-dimethylaminoazobenzene, 4-o-tolyazo-o-toluidine, benzo(a)pyrene, 7,12-dimethylbenzyl(a)anthracene, 3-methylcholanthrene, and diethylstilbestrol (DES) was studied. Six of the chemicals were used with a cell-mediated system using Chinese hamster Don-6 cells as the target cells and co-cultivated AH66-B or R1 cells as the metabolizing feeder layer. Out of 14 indirect mutagens/carcinogens tested, 11, including 5 amine derivatives, 3 azo compounds, 2 aromatic hydrocarbons and 1 steroid, induced SCEs in AH66-B and/or R1 cells. The frequency of SCEs in Don-67 cells exposed to 6 selected chemicals was substantially enhanced in the presence of AH66-B or R1 cells. For some chemicals, especially aromatic hydrocarbons, the doses required to induce SCEs in AH66-B and R1 cells were much higher than those reported for some other cell systems. Certain chemicals, eg, DES, were active inducers of SCEs in the present systems, but are known to be inactive in microbial and other test systems. The two approaches described represent simple and reliable screening assays in vitro for detection of indirect mutagens/carcinogens. (32 Refs)

23. DIFFERENTIAL EFFECT OF DEXAMETHASONE ON FRIEND LEUKEMIA CELLS INDUCED TO DIFFERENTIATE BY HEXAMETHYLENEBISACETAMIDE OR BUTYRIC ACID.

Gambari R
Inst. di Biologia Generale, Univ. di Roma, Rome, Italy
Cell Biol Int Rep; 6(4):341 1982

The effects of dexamethasone (DEX) on erythroid function in murine Friend leukemia (FL) cells, clone DS19-4, induced to differentiate by hexamethylenebisacetamide (HMBA) or butyric acid (BA) were investigated. Synthesis and translation of alpha- and beta-globin mRNA and Hb accumulation were greatly inhibited by DEX in the HMBA-induced cells. DEX had no effect on these functions in the BA-induced cells. The results suggest that HMBA and BA modulate gene expression in FL cells via a different mechanisms. The DS19-4 cells cultured with BA may share cellular properties in common with FL clones resistant to DEX inhibition of HMBA-induced erythroid differentiation. (5 Refs)

AMINO ACID ANALOGS AND MODIFIED NUCLEIC ACID CONSTITUENTS

24. PURINE NUCLEOSIDE ANALOGUES INHIBIT THE REPAIR OF RADIATION-INDUCED POTENTIALLY LETHAL DAMAGE IN MAMMALIAN CELLS IN CULTURE.

Nakatsugawa S, Sugahara T, Kumar A
Dept. Experimental Radiology, Faculty Medicine, Kyoto Univ., Kyoto 606, Japan
Int J Radiat Biol; 41(3):343-346 1982

Effects of nucleoside analogs, including 3'-deoxyguanosine, 3'-deoxycytidine, 3'-deoxyuridine, 2',3'-dideoxythymidine, and beta-D-arabinofuranosyladenine, on repair of potentially lethal damage (PLD) in irradiated cells were studied in hamster HA-1 cells in the stationary phase. Of the nucleosides tested, only purine analogs inhibited the repair of PLD significantly at relatively low doses. (10 Refs)

25. THE CYTOTOXIC AND MUTAGENIC EFFECTS OF 5-BROMODEOXYURIDINE-PLUS-BLACK-LIGHT TREATMENT IN CULTURED MAMMALIAN CELLS.

Lynn LA, O'Neill JP
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Mutat Res; 94(1):179-187 1982

The cytotoxic and mutagenic effects of bromodeoxyuridine (BrdUrd) plus black light (360 nanometer) on Chinese hamster ovary (CHO) cells were investigated. CHO cells were initially incubated with different concentrations of BrdUrd for 25 hr (conditions known to be mutagenic) prior to exposure to black light. Cultures were incubated with 0, 2, 10 and 50 uM BrdUrd and exposed to black light for 0-300 min. Black light alone showed no cytotoxic or mutagenic effects. With increasing duration of light exposure, an exponential decline in cell survival was observed with each BrdUrd concentration, and the slope of the line increased with the concentration of BrdUrd. Light exposure also resulted in mutation induction with 2 and 10 uM BrdUrd, concentrations which alone were not mutagenic, and in increases above the mutant frequency induced by 50 uM BrdUrd alone. These results indicate that the lack of mutagenicity of BrdUrd concentrations of 10 uM or less is not due to a lack of incorporation into the hypoxanthine-guanine-phosphoribosyl-transferase locus, since subsequent exposure to black light and photolysis of the incorporated BrdUrd can be detected as an increase in the frequency of thioguanine-resistant mutants. This methodology might be used to study specific-locus repair in a manner analogous to the BrdUrd-incorporation method described by Regan et al. (19 Refs)

26. AZASERINE: SURVIVAL AND MUTATION IN ESCHERICHIA COLI.

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Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL, 60439
Mutat Res; 94(1):31-38 1982

The nature of the genetic and molecular mechanisms involved in the lethal and mutagenic effects of azaserine (AZS) were investigated in Escherichia coli strain WP2 and a series of its repair-deficient mutants. Survival of cells removed from stationary-phase cultures at 18, 41, 65, and 180 hr after inoculation into minimal medium and exposure to various concentrations of AZS was biphasic with the initial and final slopes differing by approx two orders of magnitude. The magnitude of the more resistant cell fraction was strongly dependent upon the age of the culture and could be further increased with growth in nutrient broth. In 18-23 hr cultures in minimal medium, strain WP2 showed the most resistance to AZS, and the mutants deficient in only one repair function were increasingly sensitive in the order WP10, WP2s, WP5, and WP6. The doubly repair-deficient mutant strains WP100 and Bs-1 had the greatest sensitivities. When cultured on nutrient agar, the order of sensitivities of WP2 and WP10 were reversed. Under both culture conditions, the wild type strain was about 8x as resistant to AZS as was the most sensitive repair-deficient mutant. These results suggest that exposure to AZS produces lethal DNA lesions. Mutation frequencies in the excision-defective strain were about 60x those in the wild-type strain WP2, and mutation frequencies in strain WP6 were about 3x those in the wild type strain. Induced mutation was not observed in strain WP5 or WP10. AZS appears to react with DNA in vivo, either directly or indirectly, producing lesions capable of causing cell death unless repaired. Mutagenesis occurs by misrepair in the SOS repair system. (18 Refs)

27. GENETIC INTERACTIONS IN INDUCTION OF ENDOGENOUS MURINE LEUKEMIA VIRUS FROM LOW LEUKEMIC MICE.

McCubrey J, Risser R
McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706
Cell; 28(4):881-888 1982

The frequency of ecotropic murine leukemia virus (MuLV) production in cells induced with halogenated pyrimidines has been investigated in several low leukemic strains of mice. Very few BALB/c or C57BL/6 (B6) induced embryo cells produce MuLV; this low frequency increases 10 to 50 fold in cells of the BALB/c x B6 F1 hybrid. Data from backcrosses of the F1 hybrid to each parent and from BALB/c x B6 recombinant inbred strains indicate that the phenotype of enhanced MuLV production results from interaction of two unlinked loci, dominant (+/+) alleles of which are carried by either parent. Genetic tests with BALB/c x B6 recombinant inbred strains confirm this two-locus model. The loci are designated Inc-1 and Inb-1 to signify their phenotypic detection by induction and the BALB/c or B6 strain of origin, respectively. Examination of hybrids of BALB/c and of B6 with other strains indicates that strains related in pedigree to BALB/c carry Inc-1, whereas those related to B6 carry Inb-1. Identification of genetic loci that specifically interact to enhance MuLV production after exposure to halogenated pyrimidines indicates the existence of mechanisms that regulate the induction or intracellular expression of endogenous MuLV. (Author abstract) (31 Refs)

28. HEPATIC LEVELS OF S-ADENOSYLETHIONINE AND S-ADENOSYLMETHIONINE IN RATS AND HAMSTERS DURING SUBCHRONIC FEEDING OF DL-ETHIONINE.

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Carcinogenesis; 3(3):309-312 1982

The levels of S-adenosylethionine (AdoEt) and of S-adenosylmethionine (AdoMet) in the livers of weanling male rats and male and female hamsters fed ethionine for 1-6 wk were determined. In both species the hepatic contents of AdoEt were dependent upon the level of ethionine in the diet. For the 6-wk experimental period the hepatic levels of AdoEt averaged 81 ug/g liver in male hamsters fed 0.1% ethionine in the diet and 160 ug/g in those fed 0.3% ethionine; the corresponding AdoEt levels in female hamsters were 104 and 191 ug/g liver, respectively. No marked shifts in hepatic AdoEt levels were seen in either male or female hamsters although a gradual rise in hepatic AdoEt from 145 to 233 ug/g was noted in the female hamsters receiving 0.3% ethionine in the diet for 1-6 wk. AdoEt levels in the livers of rats fed 0.3% ethionine were quite variable. In rats fed the 0.1% ethionine diet the liver AdoEt levels dropped from 103 to 61 ug/g from wk 1 to 6. In animals fed the ethionine-free diet, the hepatic contents of AdoMet were relatively constant throughout the 6-wk experimental period. Chronic ethionine administration always suppressed hepatic AdoMet levels. This suppression was generally greater in animals fed the 0.1% ethionine than in those fed the 0.3% ethionine diet. Thus, the av hepatic AdoMet levels in rats, male hamsters and female hamsters receiving the 0.1% ethionine diet for 3-6 wk were 32, 18, and 45% respectively, of the corresponding AdoMet levels in animals receiving the 0.3% ethionine diet were 66, 42, and 62% of the respective control values. Feeding 0.1% ethionine to male hamsters led to exceedingly low levels of liver AdoMet (1.4-2.9 ug/g). No direct correlations could be made between the effects of ethionine feeding on the hepatic AdoEt and AdoMet levels in rats and hamsters and the previously reported differences in carcinogenicity by ethionine in these species. (26 Refs)

29. ALTERATIONS IN DNA-DEPENDENT RNA POLYMERASE I FROM RAT LIVER ACCOMPANYING ETHIONINE ADMINISTRATION.

Yamano H, Sawai Y, Thung WL, Sato F, Tsukada K
Dept. Pathological Biochemistry, Medical Res. Inst., Tokyo Medical and Dental Univ., Kandasurugadai, Chiyoda-ku, Tokyo 101, Japan
Biochem Biophys Res Commun; 105(3):799-805 1982

Repeated administration of ethionine, an hepatocarcinogen and the ethyl analogue of the amino acid methionine, was found to increase the activity of RNA polymerase I from rat liver nuclei 3-to 4-fold when given simultaneously with adenine. It is suggested that changes in RNA polymerase I levels observed after ethionine administration may constitute an important early biochemical event in the liver that triggers cellular proliferation leading to the development of neoplasia. (27 Refs)

ALIPHATIC HALOGEN COMPOUNDS

30. INHIBITION OF MICROSOMAL DRUG OXIDATIONS BY ALIPHATIC HALOHYDROCARBONS: CORRELATION WITH VAPOUR PRESSURE.

Poplawski-Tabarelli S, Uehleke H
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Xenobiotica; 12(1):55-61 1982

The effects of 12 halogenated aliphatic compounds on microsomal N-dealkylation, C-hydroxylation and N-oxidation of N-methylaniline and N-hydroxylation of p-chloroaniline were determined in closed reaction vessels. There is no correlation between the volatility of the agents investigated and their binding characteristics to oxidized or reduced microsomal cytochrome P-450. High correlation was observed between inhibition of cytochrome P-450-mediated drug oxidations and the boiling points (vapor pressure) of the individual compounds. The N-oxidation of N-methylaniline, which is not catalyzed by cytochrome P-450, did not show this correlation. Other factors eg ligand formation with reduced cytochrome P-450, lipid peroxidation and heme destruction, production of carbon monoxide, and alterations of microsomal cofactors, did not produce significant inhibition. Many artefacts occur when reaction velocities, inhibition constants and optical affinities to microsomal cytochromes are determined for volatile chemicals under uncontrolled conditions. (Author abstract) (29 Refs)

31. THE EFFECTS OF BROMOBENZENE AND CARBON TETRACHLORIDE EXPOSURE IN VITRO ON THE PHOSPHOLIPASE C ACTIVITY OF RAT LIVER CELLS.

Lamb RG, Schwertz DW
Dept. Pharmacology and Medicine, Medical Coll. Virginia, Box 217, Richmond, VA, 23298
Toxicol Appl Pharmacol; 63(2):216-229 1982

Following in vitro incubation with bromobenzene or carbon tetrachloride, intact rat hepatocytes in 1000 g cell fractions and plasma membranes exhibited a degradation of phospholipids, indicated by the conversion of membrane-bound phosphatidic acid into diacylglycerol. Bromobenzene or carbon tetrachloride treatment also caused an increase in the activity of phospholipase C. A critical factor in the cellular injury induced by these hepatotoxins may be a disruption of the cell membrane structure due to the degradation of membrane lipids by the induced phospholipase C. (29 Refs)

32. DIETARY MODIFICATION OF METABOLISM AND TOXICITY OF CHEMICAL SUBSTANCES - WITH SPECIAL REFERENCE TO CARBOHYDRATE.

Nakajima T, Koyama Y, Sato A
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Biochem Pharmacol; 31(6):1005-1011 1982

Rats were fed various test diets only on the day before sacrifice or every day for 3 wk prior to sacrifice in order to assess the effects of protein (casein), fat (a mixture of olive and corn oils) and carbohydrate (sucrose) on the liver mixed-function oxidase activity. The activity was determined by measuring metabolic rates of eight volatile hydrocarbons, ie, benzene, toluene, styrene, chloroform, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloroethylene, and trichloroethylene. Contrary to the general belief, it was found that carbohydrate, not protein or fat, regulates the metabolism of these hydrocarbons; a diet which was deficient in carbohydrate remarkably enhanced the metabolism irrespective of protein and fat contents in the diet. This conclusion was confirmed by employing two types of diet, one in which the carbohydrate was replaced by an isocaloric amount of protein or fat (thus keeping total calories of each diet constant) and the other in which the carbohydrate content was varied with protein and fat contents fixed (total calories of each diet differed from others according to the carbohydrate content). In accordance with this, dietary carbohydrate intake also exerted a remarkable influence on the hepatoxocity of carbon tetrachloride which needs to be metabolically activated to become cytotoxic; the smaller the intake, the more severe the liver injury. (Author abstract) (28 Refs)

POLYHALOGENATED RING COMPOUNDS INCLUDING INSECTICIDES

33. DISTRIBUTION OF 5'-NUCLEOTIDASE DURING HEPATOCARCINOGENESIS INDUCED BY HEXACHLOROCYCLOHEXANE IN SWISS MICE.

Bhatt DK, Nigam SK, Lakkad BC, Babu KA, Karnik AB, Thakore KN, Kashyap SK, Chatterjee SK
Natl. Inst. Occupational Health (ICMR), Meghani Nagar, Ahmedabad 380 016, India
Indian J Exp Biol; 19(12):1159-1162 1981

Male inbred Swiss mice were fed 500 ppm of hexachlorocyclohexane (BHC) for 2, 4, or 6 mo and the livers were histochemically studied for the distribution of 5'-nucleotidase (5NT). After 2 mo, hepatocytes in the periportal area showed intense enzymatic activity. Activity in the nodular part increased compared with the nonnodular part. Tumor tissue always showed very strong 5NT activity compared with the nontumor tissue. Intercellular spaces showed strong 5NT activity. As time increased, the main changes in 5NT distribution were disappearance of 5NT from the cytoplasm (persisting even after tumor development), increase in 5NT activity in the nucleus (disappearing in well developed nodules and tumors), and gradual increase in 5NT activity on the plasma membrane and intercellular space. The change in activity during hepatocarcinogenesis may be associated with the functional and constitutional aspect of the plasma membrane. The absence of cytoplasmic activity of 5NT may be associated with complete disruption of ergestroplasm during carcinogenesis, excessive accumulation of glycogen in the cytoplasm, lysosomal damage, and repression of the gene responsible for synthesis of cytoplasmic 5NT. 5NT may be a specific indicator of hepatic diseases and tumors of the liver. (22 Refs)

34. CYTOSOLIC AND NUCLEAR BINDING OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN TO THE AH RECEPTOR IN EXTRA-HEPATIC TISSUES OF RATS AND MICE.

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Eur J Biochem; 123(1):209-215 1982

Induction of aryl hydrocarbon hydroxylase (cytochrome P1-450) is mediated by the Ah receptor which initially binds inducing chemicals in the cytoplasm, after which the inducer-receptor complex translocates into the nucleus. Ah receptor can be detected and quantified by sucrose-density-gradient analysis of its binding to 2,3,7,8-tetrachloro[3H]dibenzo-p-dioxin. Labeling in vitro of cytosols from C57BL/6J mice and Sprague-Dawley rats reveals Ah receptor in several tissues, with concentrations in the rank order for C57BL/6J mice: liver greater than lung much greater than kidney approx = thymus approx = small intestine greater than prostate; for Sprague-Dawley rats: liver approx = lung approx = thymus much greater than small intestine much greater than greater than kidney. Cytosol receptor was not detectable by assays in vitro on skin, skeletal muscle, heart, brain or testis of C57BL/6J mice or Sprague-Dawley rats, nor was specific receptor detectable in cytosol from any tissue of genetically 'non-responsive' DBA/2J mice. Injection in vivo of 2,3,7,8-tetrachloro[3H]dibenzo-p-dioxin led to recovery of specific nuclear Ah receptor from liver, lung and kidney of both genetically 'responsive' C57BL/6J mice and 'non-responsive' DBA/2J mice as well as Sprague-Dawley rats. Nuclear Ah receptor concentrations were lower in DBA/2J mice than in C57BL/6J mice receiving the same dose, and nuclear receptor was detectable only with injection of high doses of 2,3,7,8-tetrachloro[3H]dibenzo-p-dioxin. Although cytosolic Ah receptor in DBA/2J mice appears to be 'defective' and cannot be detected directly by assays in vitro, recovery of specific receptor from nuclei of DBA/2J tissues implies that binding of 2,3,7,8-tetrachloro[3H]dibenzo-p-dioxin to Ah receptor does occur in vivo in these animals; this may explain the ability of 'non-responsive' DBA/2J mice to exhibit induction of aryl hydrocarbon hydroxylase when treated with the very potent inducer, 2,3,7,8-tetrachlorodibenzo-p-dioxin. (Author abstract) (12 Refs)

35. HUMAN TISSUE BURDENS OF HALOGENATED AROMATIC CHEMICALS IN MICHIGAN.

Wolff MS, Anderson HA, Selikoff IJ
Environmental Sciences Lab., Cummings Basic Sciences Building, 10 E. 102nd St., New York, NY, 10029
JAMA; 247(15):2112-2116 1982

A cross section of the population of Michigan was studied in 1978 to evaluate residual burdens of polybrominated biphenyls (PBBs), a flame-retardant chemical that had contaminated the state's food supply 5 years earlier. Levels of PBB were measured in serum specimens in 1,681 people and in adipose samples in 844. Ninety-seven percent of the adipose samples had detectable PBB concentrations. levels of PBB were highest in that part of the state where meat and dairy products had been most contaminated and were lowest in the upper peninsula, farthest from the source. Levels for the rest of the state were in between. Polychlorinated biphenyls (PCB) and 2,2'-bis(p-chlorophenyl)-1,1-dichloroethylene (p,p'-DDE), a dichlorodiphenyltrichloroethane (DDT) residue, were also measured, and variations of PBB, PCB, and p,p'-DDE levels with age and sex were investigated. (Author abstract) (18 Refs)

36. MUTAGENICITY STUDIES WITH 2,4,5-T ON BACTERIA AND MAMMALIAN GERM CELLS.

Herbold BA, Machemer L, Rohrborn G
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Teratogenesis Carcinog Mutagen; 2(1):91-101 1982

The herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) was tested for mutagenicity in an Ames mutagenicity with microsomal activation, a dominant lethal test in rats, and a cytogenetic assay of Chinese hamster spermatogonia. The 2,4,5-T contained 0.05 ppm dioxin. Salmonella strains used were TA 98, 100, 1535, and 1537, with cyclophosphamide and trypaflavine as controls. 2,4,5-T was tested at 4-2,500 ug/plate. In the dominant lethal test rats were fed 0.1, 1, or 100 mg/kg 2,4,5-T for 8 wk and then mated. Corpora lutea, dead, and viable embryos were counted 12 days after mating, and the rate of dominant lethal mutations determined. For the cytogenetic assay male Chinese hamsters were fed 0, 0.5, 5, or 50 mg/kg 2,4,5-T per day for 5 days in one test, and 0 and 500 mg/kg on the same schedule in a second test. The 2,4,5-T was not mutagenic in any of these tests. These findings are compared with tests of 2,4,5-T in other systems. (46 Refs)

37. INHIBITION OF METABOLIC COOPERATION IN CHINESE HAMSTER V79 CELLS IN CULTURE BY VARIOUS POLYBROMINATED BIPHENYL (PBB) CONGENERS.

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Dept. Pediatrics and Human Development, Coll. Medicine, Michigan State Univ., East Lansing, MI, 48824
Carcinogenesis; 3(2):181-185 1982

Using an in vitro assay system to measure a form of cell-cell communication in Chinese hamster V79 cells, several purified polybrominated biphenyl (PBB) congeners were analyzed for their ability to affect colony-forming ability and 'metabolic cooperation' in these cells. Results clearly demonstrate the assay's ability to distinguish differences in the cytotoxic and metabolic cooperation-inhibiting properties of these congeners related to their structure. It appears that if a carbon ortho to the bridge carbon of each phenyl ring is brominated, the molecule has the property by which metabolic cooperation is inhibited. The results suggest that several PBB congeners share at least one property associated with several known tumor promoters, such as the phorbol esters. Although we have not ruled out that the mixture of PBB congeners might contain initiators or that various PBB metabolites would be mutagen/initiators, based on these and other results, it was concluded that the reported carcinogenic potential of PBB seems to be mediated by its action as a tumor promoter, rather than as a complete carcinogen or an initiator. (Author abstract) (54 Refs)

38. PHENOXY ACID HERBICIDES CAUSE PEROXISOME PROLIFERATION IN CHINESE HAMSTERS.

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Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Scand J Work Environ Health; 8(1):70-73 1982

Chinese hamsters 12-20 weeks old were given by gavage saline dilutions of commercial herbicides containing either 2,4-dichlorophenoxyacetic acid (2,4-D) or 4-chloro-2-methylphenoxyacetic acid (MCPA). No other active ingredient was present. Nine daily doses were given at 100 mg/kg. The positive control group received clofibrate (CF: 100 mg/kg/day sc, x 7). All test and control animals were sacrificed 1 day after the last dose. Peroxisomes were chemically localized in liver samples and the areas examined by electron micrographic projection. MCPA and CF significantly increased the size of the peroxisomes (p less than 0.001). CF and 2,4-D also increased significantly the number of peroxisomes (p less than 0.001). CF is chemically related to the two herbicides and has been suggested to exert its carcinogenic action through excess production and/or breakdown of hydrogen peroxide resulting in DNA damage. It is suggested that the increased incidence of soft tissue sarcoma and malignant lymphoma related to exposure to phenoxy acid herbicides may derive from the same mechanism, since both herbicides tested increase the size of or proliferate peroxisomes. (11 Refs)

BENZENE DERIVATIVES

39. MUTAGENICITY IN SALMONELLA TYPHIMURIUM AND STRUCTURE-ACTIVITY RELATIONSHIPS OF WASTEWATER COMPONENTS EMANATING FROM THE MANUFACTURE OF TRINITROTOLUENE.

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SRI International, Menlo Park, CA, 94025
Environ Mutagen; 4(2):163-179 1982

Mutagenic screening of 36 polynitroaromatic compounds in wastewater of a plant that manufactures 2,4,6-trinitrotoluene (TNT) was accomplished with strains TA1535, TA1537, TA1538, TA98, and TA100 of Salmonella typhimurium using the Ames test with and without microsome S-9 mix from Sprague-Dawley rats. Five dose levels ranging up to 5,000 ug/plate were used. Combinations of the wastewater components to yield a synthetic condensate blend were mutagenic in all 5 strains with and without metabolic activation. The most active compounds as determined by mutagenic potency with strain TA100 were 2,4,5-TNT greater than 3,5-dinitroaniline greater than 1,3,5-trinitrobenzene, which occur as trace elements in the discharge from munitions production facilities. The three components represent 0.6% of the waste, but account for approx 20% of the mutagenic potency of the wastewater. Over 80% of the compounds tested were mutagenic in either strain TA98 or TA100. Generally compounds showing activity with or without S-9 were more mutagenic in the absence of metabolic activation. Mutagenicity of polynitroaromatic compounds in S typhimurium depends primarily on the nitroreductase activity of the strains; enzymatic reduction is favored by para orientation of nitro groups in TNTs, aminodinitrotoluenes, and dinitrotoluenes. (20 Refs)

40. THE ROLE OF MONONITROCHLOROBENZENE AS A CONTAMINANT IN DINITROCHLOROBENZENE.

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J Am Acad Dermatol; 6(3):325-327 1982

The results of dinitrochlorobenzene (DNCB) screening for mutagenicity in the Ames assay are inconsistent. No in vivo tests have as yet disclosed carcinogenic activity for DNCB. It is suggested that the positive results with DNCB in some Ames assays may have been related to contamination of the sample with mononitrochlorobenzenes (MNCB), which are known carcinogenic precursors. Analysis of three commercial DNCB samples disclosed no MNCB. In view of the high cutaneous absorption of topically applied DNCB in acetone (up to 65%) and the use of DNCB in the treatment of some skin diseases, greater attention must be paid to the purity of the DNCB sample. Further mutagenicity and carcinogenicity assays using highly purified DNCB are necessary. (19 Refs)

41. GENOTOXICITY OF SAFROLE-RELATED CHEMICALS IN MICROBIAL TEST SYSTEMS.

Sekizawa J, Shibamoto T
Ogawa and Co. Ltd., 1-12-3 Niitaka, Yodogawa-Ku, Osaka, Japan
Mutat Res; 101(2):127-140 1982

Genotoxicities of safrole, nine related compounds (anethole, cinnamaldehyde, cinnamyl alcohol, estragole, methyl eugenol, eugenol, isoeugenol, isosafrole, piperonal), five essential oils (anise oil, cassia oil, cinnamon bark oil, clove oil, fennel oil), and one oleoresin (pimenta oleoresin) were examined in the Bacillus subtilis DNA repair test (Rec assay) without S9 activation, in the Escherichia coli WP2 uvrA reversion test, and in a modified Ames test. No test compounds induced a significant increase in revertant numbers in either Salmonella tester strains or with E coli WP2 uvrA in the absence of S9. Anethole was the only compound that showed a significant increase in revertants in the presence of S9. A clear dose-dependent increase of induced mutation frequencies of TA100 cells was observed with anethole. All chemicals except anethole, estragole, and isosafrole were positive in the Rec assay without S9. The results are discussed in relation to the nature of the problems encountered with each test method. (20 Refs)

42. PRELIMINARY EXPERIMENTAL CONTRIBUTION TO THE STUDY OF POSSIBLE CARCINOGENIC ACTIVITY OF TWO HERBICIDES CONTAINING ATRAZINE-SIMAZINE AND TRIFLURALIN AS ACTIVE PRINCIPLES.

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Pathologica; 73(1027):707-721 1981

The carcinogenicity and mutagenicity of the herbicides Fogard S and Treflan were studied in vivo in female Swiss albino mice and in vitro in human lymphocyte cultures. The active principles in Fogard S are atrazine (25%) and simazine (37.5%). The active principle in Treflan is trifluralin (44.5%). Groups of 25 mice each received 0.25 ml of 2 ppm Fogard S or Treflan ip or sc, 13x at 3-day intervals. One animal from each group was killed every 15 days up to 7 mo. Necropsies were performed when possible on all animals. One mouse from the sc-Fogard S group, five from the ip Fogard S group, and four from the ip Treflan group were lost to cannibalism and could not be examined. Malignant lymphomas (ML) were found in three mice and mesothelioma (MT) in one mouse from the sc Fogard S group. ML was found in two mice from the ip Fogard S group. ML was found in five mice and MT in one from the sc Treflan group. ML was found in three mice and MT in three mice from the ip Treflan group. Cultures of human lymphocytes were stimulated with phytohemagglutinin and then exposed to 0.2, 0.1, or 0.05 cc of 2 ppm Treflan or 0.2, 0.05, or 0.01 cc of 2 ppm Fogard S. Fogard S did not produce abnormalities in morphology or chromosomal variations. At the higher dose, Fogard S produced a slight decrease in mitoses. Treflan produced significant decreases in the number of mitoses with increasing dose. Chromosomal abnormalities were produced in increased frequencies at the lowest dose. Results indicate a correlation between in vivo administration of either herbicide and tumor formation, as well as a correlation between in vitro Treflan administration and genetic abnormalities. (23 Refs)

43. SUBSTITUENT EFFECTS ON THE MUTAGENICITY OF PHENYL GLYCIDYL ETHERS IN SALMONELLA TYPHIMURIUM.

Neau SH, Hooberman BH, Frantz SW, Sinsheimer JE
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Mutat Res; 93(2):297-304 1982

The Ames test for mutagenicity was used with glycidyl phenyl ether, p-bromophenyl 2,3-epoxypropyl ether, 2,3-epoxypropyl p-methoxyphenyl ether, p-chlorophenyl 2,3-epoxypropyl ether, p-tert-butylphenyl 2,3-epoxypropyl ether, 2,3-epoxypropyl p-tolyl ether, and 1,2-epoxy-3-(p-nitrophenoxy)-propane. All seven compounds were mutagenic in both strains TA100 and TA1535, with the exception of the tert-butyl form, which was not active in TA1535. The Hammett sigma constants reported for the ionization of benzoic acid were compared to the mutagenicity of the phenyl glycidyl ethers. A reasonable correlation of mutagenicity in both strains was evident as compared to the Hammett sigma values for the para substituents. Mutagenicity generally increased with the strength of the electron-withdrawing substituent, particularly for the bromo, chloro, and nitro groups. (13 Refs)

44. MECHANISM OF BENZENE TOXICITY. EFFECTS OF BENZENE AND BENZENE METABOLITES ON BONE MARROW CELLULARITY, NUMBER OF GRANULOPOIETIC STEM CELLS AND FREQUENCY OF MICRONUCLEI IN MICE.

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Chem Biol Interact; 39(2):129-138 1982

The effects of benzene and benzene metabolites (hydroquinone and catechol) on bone marrow cellularity, number of granulopoietic stem cells and on the frequency of micronuclei in polychromatic erythrocytes were investigated in mice. The dose-effect curve for benzene revealed that there was a threshold dose (approx 100 mg benzene/kg body wt/day injected sc on 6 consecutive days) above which severe toxicity occurred in all three parameters. Also hydroquinone gave rise to adverse effects in the parameters studied, but the sequence of occurrence was different from that observed with benzene. These data are interpreted to indicate that hydroquinone is a hemotoxic metabolite of benzene in mice in vivo, but that other metabolites, or benzene itself, also probably contribute to the toxicity. Catechol gave no effects. However, due to acute effects like tremor and convulsions only rather low doses could be tested. Simultaneous administration of toluene dramatically reduced the toxicity of benzene, but gave only a small reduction of the hydroquinone-induced effects. (Author abstract) (25 Refs)

45. A STUDY OF AROMATIC NITRO COMPOUNDS FOR THE SELECTION OF CANDIDATES FOR CARCINOGEN BIOASSAY.

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J Environ Sci Health [A]; 17(1):75-128 1982

The class of aromatic nitro compounds was studied in order to nominate chemicals to the National Cancer Institute as candidates for carcinogen bioassay. Scope was defined as commercially significant organic compounds that contain an aromatic, six-membered carbocyclic system with at least one direct substitution of the nitro (NO_2) functionality. Potential carcinogenicity was evaluated from published reports. After application of several qualifying criteria relating to previous, current, or planned carcinogenicity tests and to commercial significance, a preliminary candidate list of 441 chemicals was reduced to 210 chemicals. Based upon consideration of both the suspicion of possible carcinogenic activity and evidence indicating potential exposure, the following 14 chemicals were nominated: 4-chloro-2-nitroaniline, 2,4-dinitroaniline, 4-nitroaniline, benefin, 2-bromo-4,6-dinitroaniline, 2-nitroanisole, nitrobenzene, 4,4'-dinitro-1,1'-stilbenedisulfonic acid, 1,8-dihydroxy-4,5-dinitroanthraquinone, C.I. Pigment Red 3, C.I. Pigment Orange 5, C.I. Pigment Red 23, C.I. Pigment Yellow 74, and 2-amino-6-nitrobenzothiazole. (54 Refs)

DRUGS, COSMETICS, DETERGENTS AND OTHER COMMERCIAL MATERIALS

46. IN VIVO ASSESSMENT OF IMMUNOTOXICITY.

Munson AE, Sanders VM, Douglas KA, Sain LE, Kauffmann BM, White KL
Dept. Pharmacology, Medical Coll. Virginia, Richmond, VA, 23298
Environ Health Perspect; 43:41-52 1982

A basic toxicological approach is described for assessing the risk of a chemical perturbing the immune system. CD-1 mice were exposed for 14 or 90 days to one of several chlorinated hydrocarbons: 1,2-dichloroethane, 1,2-dichloroethylene or 1,1,2-trichloroethylene. Other mice were exposed to dexamethasone, a known immunosuppressive agent. The immune system is evaluated against a background of the more standard toxicological parameters such as fluid consumption, body and organ weights, hematology, clinical chemistry, and blood coagulation. Reported here are the results for the male mice after 14-day exposure to three chlorinated hydrocarbons and after 90-day exposure to 1,2-dichloroethane and dexamethasone. Acute toxicity studies were performed to provide a basis for doses used in the subchronic studies. The LD50 values are reported. The status of the humoral immune system was determined by measuring the number of IgM spleen antibody-forming cells to sRBC, the serum antibody level to sRBC, and the lymphocyte response to the B-cell mitogen, LPS. The data suggest that dexamethasone administered in the drinking water is nonspecifically cytotoxic to the spleen cells. Cell-mediated immunity was assessed by measuring the DTH response to sRBC and the response to the T-lymphocyte mitogen, concanavalin A. Dichloroethane did not alter the functional activity of the reticuloendothelial system, as measured by the vascular clearance rate and tissue uptake of 51Cr sRBC. In the case of dexamethasone exposure, only the spleen and thymus showed decreased uptake of 51Cr sRBC, which was directly related to decrease in size. The approaches and results from these types of studies provide a basis for judging a chemical's potential risk to the immune system. (7 Refs)

47. STRUCTURE-MUTAGENICITY RELATIONSHIP IN ALPHA,BETA-UNSATURATED CARBONYLIC COMPOUNDS AND THEIR CORRESPONDING ALLYLIC ALCOHOLS.

Lutz D, Eder E, Neudecker T, Henschler D
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Mutat Res; 93(2):305-315 1982

The mutagenicities of 16 allylic alcohols and their carbonylic derivatives commonly used in industry were determined using the Ames test with Salmonella typhimurium TA100 in the modified suspension test of Rannug et al. Of the alcohols, allyl alcohol proved to be a potent mutagen (750 revertants/umole without S9 mix; 145 revertants/umole with S9); the next higher homolog and two isomers showed little or no mutagenic effect. Glycidol, the epoxide of allyl alcohol was distinctly mutagenic, but much less so than the non-epoxidized alcohol. Acrolein, crotonaldehyde, 2-methylacrolein, and methylvinyl ketone were strongly mutagenic without S9 mix; all but acrolein were also distinctly mutagenic with S9 mix. 2-cyclohexene-1-one was slightly mutagenic; cinnamylaldehyde and citral were not at all mutagenic according to the modified Ames test. In general mutagenicity was highest in the lowest members of homologous series, both of allylic alcohols and their corresponding unsaturated carbonyl compounds. There was a positive correlation between electrophilicity and direct mutagenicity. S9 mix did not increase mutagenicity in non-mutagenic compounds, but more or less inactivated the mutagenic compounds depending on their electrophilic properties. (23 Refs)

48. MODERN DEVELOPMENTS IN MUTAGENESIS.

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J Chem Technol Biotechnol; 32(1):354-364 1982

The increase in mutation yield was studied in Penicillium chrysogenum and Streptomyces clavuligerus. Five mutants of S clavuligerus and one of P chrysogenum were isolated on the basis of increased sensitivity to far UV light (FUV). The sensitivities of these mutants and other mutagens are presented. The mutation rates of these strains in response to a range of mutagens were estimated by various forward mutation systems, including mutation to acriflavine, rimfampicin, ethidium bromide, or 5-fluorouracil resistance and 2-thioxanthine non-utilization. The mutational responses of the UV sensitive (UVs) strains and their parents are illustrated. No differences were detected in P chrysogenum between the UVs-strain and its parent in induced mutation frequency after FUV or ethylmethanesulphonate treatment. A significant difference was observed after gamma-irradiation where the UV-strain showed a reduced mutational yield relative to its parent. All five strains of S clavuligerus were altered in mutational response to FUV. In wild-type strains of S clavuligerus caffeine (CF) increased FUV mutation and decreased survival after irradiation. Unlike S clavuligerus where CF was added after irradiation, the spores of P chrysogenum had to be pretreated in CF soln prior to irradiation. CF increased the induced-mutation frequency of the UVs strains and its parent, the effect being greatest in the UVs strain. CF led to higher survival levels in the sensitive strain and decreased survival in its parent. Processes such as liquid holding and nalidixic acid treatment, which have been shown to affect DNA replication, caused an increase in FUV-induced mutation in P chrysogenum. A similar effect on mutation frequency was observed in S clavuligerus when spores were liquid held. (54 Refs)

49. DNA CONTENT OF CELLS WITH GENERALIZED CHROMOSOME SHATTERING INDUCED BY ULTRAVIOLET LIGHT PLUS CAFFEINE.

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Mutat Res; 94(1):133-142 1982

The results of flow cytometric analyses of DNA content of UV and caffeine-treated Chinese hamster ovary (CHO) cells are reported. CHO cells growing asynchronously were exposed to 5.0 Joules/square meter UV (254 nanometer) and then incubated with or without 2 milliM caffeine. Very few generalized chromosome shattering (GCS)-cells were observed in control cultures or in cultures treated with UV or caffeine alone.

However, the GCSm (number of cells with GCS-like appearance/number of cells with condensed, chromosome-like chromatin x 100) and GCSt (%GCSm x mitotic index) increased sharply to 86 and 10, respectively, after treatment with UV plus caffeine. Fluorescence distributions for control, UV-treated and caffeine-treated cells were very similar. Peak B in fluorescence distributions of UV- and/or caffeine-treated cells corresponded to a normal G2M content. All GCS-like cells were found to have the G2M DNA content. These results suggest a subtle process resulting in failure of normal chromosome condensation after most or all of the DNA has been replicated in GCS-like cells. (29 Refs)

50. STUDIES ON TUMORIGENICITY AND METABOLISM OF ISONIAZID IN MICE AND RATS.

Mate NB, Maru GB, Bhide SV
Carcinogenesis Div., Cancer Res. Inst., Tata Memorial Centre, Bombay 400 012, India
Indian J Exp Biol; 19(11):1037-1039 1981

The carcinogenicity and metabolism of isoniazid (INH) and its effect on nucleic acid and protein biosynthesis were studied in Wistar rats and Swiss mice. Mice received 1.1 mg INH/day and rats 4 mg/day by gavage, or mice and rats received 0.09 mg/kg body wt ip. Rats treated with INH were refractory to the tumorigenic effect of the drug. INH was tumorigenic only in mice, with a 55% incidence of lung tumors. In mice, there was a significant increase in ammonia levels occurred 1 hr after administration and remained high even at 4 hr; no increase in ammonia was noted at any time in rats. The concentration of circulating INH was much higher in mice than in rats at different time points. Levels of acetyl isoniazid were higher in rats than mice, suggesting faster acetylation in rats than mice. In mice, circulating levels of mono and diacetyl hydrazines remained high for longer periods than in rats. INH and hydrazine sulfate inhibited DNA synthesis in lung tissue of mice only, while not affecting DNA biosynthesis in mouse liver and the lung and liver of rats. Acetyl isoniazid had no inhibitory effect on any of the tissues of the rat. Two hr after INH administration, protein biosynthesis was not affected in liver and lung tissues of mice, although 24 hr after administration protein synthesis was inhibited in lung tissue. Rat tissues were not affected with respect to DNA synthesis. (24 Refs)

51. ENHANCED SENSITIVITY TO THE LETHAL AND MUTAGENIC EFFECTS OF PHOTOSENSITIZING ACTION OF CHLORPROMAZINE IN ETHYLENEDIAMINETETRAACETATE-TREATED ESCHERICHIA COLI.

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Photochem Photobiol; 35(4):591-592 1982

Ethylenediaminetetraacetate (EDTA) treatment of Escherichia coli H/r30 (Arg-) enhanced cell sensitivity to the lethal and mutagenic effects of the photosensitizing action of chlorpromazine (CPZ). The most obvious effect of EDTA on the fluence-survival curve was an elimination of the shoulder. In the absence of EDTA, CPZ plus near-UV radiation did not induce the reversion from arginine-auxotroph to autotroph of E coli H/r30. However, when EDTA (5 mM)-treated cells were subjected to CPZ plus near-UV radiation, the induced reversion frequency increased with time of irradiation. It is concluded that the enhanced penetration of CPZ into E coli cells by EDTA facilitates the drug binding to DNA within the cells upon near-UV irradiation and that this is the cause for the enhanced photosensitized lethal and mutagenic effects of CPZ. (Author abstract) (9 Refs)

52. CARCINOGENICITY AND TOXICITY OF 1,2-DIBROMOETHANE IN THE RAT.

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Toxicol Appl Pharmacol; 63(2):155-165 1982

The chronic effects of 1,2-dibromoethane (ethylene dibromide, EDB) were investigated in rats. Three experimental groups were studied: (1) inhalation of 20 ppm EDB over an 18-mo period, (2) 0.05% disulfiram (DS) in the diet for 18 mo, and (3) combined treatment of 20 ppm EDB + 0.05% DS. Rats receiving DS only showed less body wt gain than controls or EDB-exposed rats over the 18-mo period. Rats receiving EDB + DS had lower wt gain than animals receiving either EDB or DS alone. A correlation between low food consumption and low body wt gain was found in rats treated with DS or DS + EDB. EDB-treated or EDB + DS-treated rats exhibited high mortality compared with control rats or those treated with DS alone. While hematological findings were normal for EDB-treated rats, EDB + DB treatment resulted in low hematocrit, hemoglobin, and red blood cell counts. Male rats treated with DS alone did not exhibit any significant histopathological changes except for a higher incidence of hemosiderosis of the spleen; females had a higher incidence of mammary tumors and of hemosiderosis of the spleen. Rats inhaling EDB alone had a higher incidence of tumors, in one or both sexes, in the spleen, adrenal, subcutaneous mesenchymal tissue, and mammary gland compared to controls. Combined treatment with EDB + DS caused an increased incidence of tumors in one or both sexes, in the liver, kidneys, thyroid, lungs, and spleen compared to treatment with either EDB or DS alone. Combined treatment also caused a higher incidence of atrophy of the testes and spleen compared to treatment with EDB alone. These results indicate that DS, a drug used in the treatment of chronic alcoholism, enhances the toxicity and carcinogenicity of EDB. Such an effect may be significant in evaluating the hazards of industrial exposure to EDB in workers who are being treated in alcohol control programs. (37 Refs)

53. THE SIGNIFICANCE OF DNA CROSS-LINKING TO CIS-DIAMMINEDICHLOROPLATINUM(II)-INDUCED CYTOTOXICITY IN SENSITIVE AND RESISTANT LINES OF MURINE LEUKEMIA L1210 CELLS.

Strandberg MC, Bresnick E, Eastman A
Dept. Biochemistry, Vermont Regional Cancer, Univ. Vermont, Coll. Medicine, Burlington, VT, 05405
Chem Biol Interact; 39(2):169-180 1982

The cross-linking of DNA by cis-diamminedichloroplatinum(II) (cis-DDP) has been studied in a murine leukemia L1210 line (L1210/0) and a 30-fold resistant subline (L1210/DDP2) utilizing the technique of alkaline elution. The kinetics of cross-link formation were similar in both cell lines. After 1-hr treatment with cis-DDP, cross-linking continued to increase to a maximum at 12 hr posttreatment. Although cross-linking decreased by 24 hr some lesions were seen to persist. After 72 hr interstrand cross-links were completely removed by both cell lines; however, 50% of the DNA-protein cross-links still remained in the sensitive cells even though they were undetectable in the resistant subline. To correlate cross-linking with cytotoxicity, a range of drug concentrations were used for concomitant growth inhibition studies and alkaline elution analyses. In addition to the 30-fold resistant sublines, two other sublines developed in our laboratory which show 20-and 50-fold resistance to cis-DDP were included in these determinations. All the resistant sublines exhibited the same degree of cross-linking at the same applied drug doses although these doses elicited markedly different cytotoxicities; cross-linking varied only with applied drug concentrations. The degree of cross-linking in L1210/0 was also directly related to the dose of cis-DDP. However, the sensitive cell line displayed equivalent total cross-linking at a five-fold lower applied dose. This may implicate an uptake phenomenon as a contributor to resistance. However, such a phenomenon can account for only part of the resistance observed as there existed six-fold more total cross-links and nine-fold more interstrand cross-links in L1210/DDP2 at doses that were equitoxic to L1210. This suggests the existence of a more critical cytotoxic lesion that was not detectable by alkaline elution, probably intrastrand cross-links. Resistance could be due to a differential removal of these lesions. (Author abstract) (31 Refs)

54. IN VITRO IMMUNOTOXICOLOGICAL ASSAYS FOR DETECTION OF COMPOUNDS REQUIRING METABOLIC ACTIVATION.

Tucker AN, Sanders VM, Hallett P, Kauffmann BM, Munson AE
Dept. Pharmacology, Medical Coll. Virginia, Richmond, VA, 23298
Environ Health Perspect; 43:123-127 1982

A system for metabolic activation of cyclophosphamide (CP), consisting of a crude microsomal fraction of mouse liver and necessary cofactors (S9 mix), was interfaced with three murine cell culture assays for immunotoxicity. These assays were: the Mishell-Dutton assay for in vitro antibody formation, splenic lymphocyte responsiveness to mitogens and bone marrow cell cultures. There was no effect of CP at doses up to 261 ug/ml (1 mM) on any of the parameters measured unless S9 mix was included. Much greater potency was achieved if the S9 mix was prepared from livers of mice pretreated with phenobarbital. Under these conditions a dose-related inhibition of plaque-forming cells (PFC) in the Mishell-Dutton assay was observed, yielding an ED50 of 6.3 ug/ml. When splenic lymphocytes were exposed to CP in the presence of induced S9 mix, a dose related inhibition of the response to the B-cell mitogen, lipopolysaccharide (LPS), and to the T-cell mitogen, concanavalin A (Con A), was observed. For the optimum LPS concentration, the ED50 for CP was 8.1 ug/ml; for the optimum concentration of Con A, the ED50 was 6.7 ug/ml. DNA synthesis was not inhibited by the doses used. When bone marrow cells were exposed to CP in the presence of induced S9 mix, the stem cell population, enumerated by colonization in semisolid medium, was reduced in a dose-dependent manner, with an ED50 of 5.2 ug/ml. Again, DNA synthesis was not affected unless higher doses of CP were used. (Author abstract) (10 Refs)

55. DNA REPAIR AND THE GENETIC EFFECTS OF THYMIDYLATE STRESS IN YEAST.

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NIEHS, Lab. Moleculair Genetics, P.O. Box 12233, Research Triangle Park, NC, 27709
Mutat Res; 93(2):353-375 1982

Resistance of certain rad mutants of Saccharomyces cerevisiae strains to thymineless death induced by aminopterin + sulfonamide is described. Defects in excision (rad3) or RAD6-dependent repair (rad6, rad18) appear to decrease the lethality and recombinagenicity of antifolate treatment. The results suggest a mechanism to explain one type of acquired resistance to methotrexate in mammalian cells. (48 Refs)

56. METABOLISM, DISTRIBUTION, AND EXCRETION OF THE FLAME RETARDANT, TRIS(2,3-DIBROMOPROPYL) PHOSPHATE (TRIS-BP) IN THE RAT: IDENTIFICATION OF MUTAGENIC AND NEPHROTOXIC METABOLITES.

Lynn RK, Garvie-Gould C, Wong K, Kennish JM
Dept. Pharmacology, Oregon Health Sciences Univ., Portland, OR, 97201
Toxicol Appl Pharmacol; 63(1):105-119 1982

Metabolism and distribution of tris(2,3-dibromopropyl) phosphate (Tris-BP) were followed in male Sprague-Dawley rats for 5 days after iv injection of 14C-Tris-BP. Approx 58% of radiolabel was excreted within 24 hr, and 86% by 5 days. At this time approx 9% of the dose remained in the body (95% recovery). Studies in several animals with exteriorized bile ducts showed that approx 34% of the dose was excreted in the bile at 24 hr, but that a minimum of 74% of this was reabsorbed. High pressure liquid chromatography demonstrated numerous radiolabeled components, of which bis(2,3-dibromopropyl) phosphate (Bis-BP) and 2,3-dibromopropanol (DBP) were identified. Tris-BP disappeared rapidly in tissues and was undetectable at 8 hr, but the half-life of Bis-BP was relatively long. Bis-BP concentrated in lung, muscle, fat, and especially blood, where it accounted for approx 90% of the radiolabel at 30 min and 8 hr. At 5 days the concentration of radiolabel was highest in the kidneys, 11x the av whole body concentration. This may be related to the polyuria induced by large doses of Tris-BP. In Ames mutagenicity testing on TA100 and TA1535, with microsomal activation, Tris-BP was most mutagenic, with Bis-BP and DBP approx equal at all concentrations except the highest (1,000 nanomole/plate), where Bis-BP was approx 80% more active. Previous work on Tris-BP is discussed and compared with these findings. (21 Refs)

57. EFFECT OF DIAZEPAM ON HEPATOCARCINOGENESIS IN THE RAT.

Hino O, Kitagawa T
Dept. Pathology, Cancer Inst., Tokyo 170, Japan
Toxicol Lett; 11(1/2):155-157 1982

The tumor promoting ability of diazepam on the number and size of enzyme altered islands (EAI) in rat liver was investigated. Ten male Donryu rats were fed a diet containing 500 ppm diazepam (50 mg/kg/day) after initiation with 0.06% 3'-methyl-4-(dimethylamino)-azobenzene. Liver tissue was subsequently examined for ATPase-deficient islands (greater than 50 microns in diameter) at wk 16. Mean EAI values in the treated group were 8.64/square cm, compared to control values of 9.76/square cm. Diazepam induced neither cytomegaly nor reduction of canalicular ATPase activity in the centrolobular hepatocytes. Diazepam is apparently not a tumor promoter like phenobarbital. (14 Refs)

58. STUDIES OF DNA DAMAGE AND CELL DEATH IN EMBRYONIC LIMB BUDS INDUCED BY TERATOGENIC EXPOSURE TO CYCLOPHOSPHAMIDE.

Manson JM
Dept. Enviornmental Health, Univ. Cincinnati, Cincinnati, OH
Teratogenesis Carcinog Mutagen; 2(1):47-59 1982

DNA damage was measured in limb buds from mouse embryos exposed to cyclophosphamide (CP) in utero. Pregnant ICR mice were given 20 mg/kg CP ip on day 11 of pregnancy, and limb buds were taken from analysis at 1, 5, 24, 48, and 72 hr. This dose of CP resulted in 30% embryolethality, and

85% of the survivors had major forelimb malformations. DNA damage was determined by alkaline elution without prelabeled DNA and measured as retention on a filter. Total DNA content was analyzed from right forelimbs, alkali-labile DNA from left forelimbs. The CP caused a slight excess of necrosis at 5 hr and massive necrosis at 24, but not excess at 48 or 72 hr. There was a trend towards increasing DNA damage with time, with the greatest differences occurring at 48 and 72 hr. There was not a significant difference between mean retention values, but there was significantly increased variance in all retention values except at 1 hr. Results suggest that the CP treatment caused heritable DNA alterations in surviving cells. (17 Refs)

59. EFFECTS OF ALKYLATING AGENTS ON THE DNA REPLICATION OF CULTURED YOSHIDA SARCOMA CELLS.

Van Der Steen J, Van Wichen BH, Benckhuysen C

Div. Experimental Chemotherapy and Radiotherapy, Antoni Van Leeuwenhoek-Huis, The Netherlands Cancer Inst., Amsterdam, The Netherlands

Chem Biol Interact; 39(2):191-204 1982

Logarithmically growing Yoshida sarcoma cells were treated for 1 hr with low (2 decades cell kill) or high (more than 6 decades cell kill) doses of alkylating agent. Pulse and chase labeled DNA from treated cells were studied by alkaline sucrose gradient centrifugation. Nitrogen mustard (HN-2), 4-hydroperoxycyclophosphamide (CY-OOH), melphalan (L-PAM) and chlorambucil (CA) had no effect on the elongation rate of newly replicated DNA, both at low and high doses, although per cell the rate of DNA synthesis declined as inferred from the rates of [3H]thymidine incorporation compared to the increase in numbers of S phase cells in the treated populations. It is concluded that these drugs act specifically on the initiation step of the DNA replication, leaving chain elongation undisturbed. At low doses the chemically related sulfur mustard (SM) had also no effect on the maturation of new DNA but at high doses a decreased elongation rate was observed. A transient inhibition of chain growth was observed following treatment with a low dose of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU). In contrast, the intercalating agent adriamycin showed a severe but delayed effect resulting in an almost complete block of the maturation. (Author abstract) (24 Refs)

60. LEUKAEMOGENIC AND MUTAGENIC ACTIVITY OF THE BUTYROPHENON, 4-[4-(4-CHLOROPHENYL)-4-HYDROXY-1-PIPERIDINYL]-1-(4 FLUOROPHENYL)-1-BUTANONE (HALOPERIDOL).

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Carcinogenesis; 3(2):223-224 1982

Development of mainly monocytic-myeloid leukemias was observed in two strains of mice upon ip administration of 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4 fluorophenyl)-1-butanone (haloperidol), an antipsychotic drug. Haloperidol was also shown to be mutagenic in the Ames Salmonella test system. (Author abstract) (7 Refs)

61. APPLICATION OF TUMOR, BACTERIAL AND PARASITE SUSCEPTIBILITY ASSAYS TO STUDY IMMUNE ALTERATIONS INDUCED BY ENVIRONMENTAL CHEMICALS.

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Environ Health Perspect; 43:81-88 1982

Model systems to study the effects of chemicals of environmental concern on bacterial and parasitic diseases as well as the immunosurveillance and destruction of transplantable tumor cells were described and evaluated. Studies were conducted in female B6C3F1 mice following adult or pre/postnatal exposure to several prototype chemicals. The prototype chemicals employed included the synthetic estrogen diethylstilbestrol (DES), the polycyclic aromatic hydrocarbon benzo(a)pyrene (B[a]P), and the carcinogenesis promoting agent 12-O-tetradecanoylphorbol-13-O-acetate (TPA). The host resistance models employed depend primarily on functional thymus-dependent immunity, although humoral immunity is suggested to have a role in the parasite model as well. These models include subcutaneous challenge with a dose of PYB6 tumor cell causing a 10-20% incidence (TD10-20) of tumor; intravenous challenge with B16 melanoma cells; challenge with a dose of Listeria monocytogenes causing a 10-20% incidence of mortality (LD10-20); challenge with a dose of Escherichia coli lipopolysaccharide endotoxin causing a 10-20% incidence of lethality (LD10-20); and challenge with larvae of Trichinella spiralis for parasite expulsion kinetic studies. Increased mortality was observed following Listeria monocytogenes challenge in DES-exposed mice. The data suggest that the increased Listeria susceptibility found following DES exposure may result from a T-cell defect. Preliminary data, using the B16 melanoma intravenous challenge model and 125IUdR to quantitate tumor mass revealed this model was sensitive to non-specifically activated macrophage kill. DES treated mice with activated macrophages did not demonstrate increased tumor mass, while mice exposed to TPA or the potent immunosuppressive agent cyclophosphamide had a significantly increased tumor mass in their lungs. (49 Refs)

62. SOME PROPERTIES OF THE TRIPLET EXCITED STATE OF THE PHOTOSENSITIZING FUROCOUMARIN: 3-CARBETHOXYPSORALEN.

Ronfard-Haret JC, Averbeck D, Bensasson RV, Bisagni E, Land EJ

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Photochem Photobiol; 35(4):479-489 1982

The compound 3-Carbethoxypsoralen (3-CPs) has been tested in the photochemotherapy of psoriasis. It only forms monoadducts with DNA and is being considered as a non-carcinogenic alternative to 8-MOP which itself forms DNA cross-links that are difficult to repair. Using laser flash photolysis or pulse radiolysis, the triplet state of 3-CPs, a possible intermediate in photosensitization, has been generated in several solvents: ethanol, water and benzene. The triplet lifetime, extinction coefficient and quantum efficiency of formation have been measured. Triplet reactivities towards (i) the solvents used, (ii) 3-CPs, (iii) oxygen, (iv) tryptophan and (v) tyrosine, leading, respectively, to photoadditions with water, ethanol and 3-CPs, to 1O2, semioxidized tryptophan and semioxidized tyrosine, (vi) thymine and (vii) uracil have been investigated. The dark binding of 3-CPs to DNA has been studied by comparing the reactivity of e-aq with free 3-CPs, free DNA and the 3-CPs-DNA complex. Some photophysical and photochemical properties of 4',5'di-hydro-3-carbethoxypsoralen (DH-3-CPs), model of the main fluorescent photoproduct of 3-CPs, have also been investigated. Biological consequences of the photochemical properties of 3-CPs and DH-3-CPs have been studied in a cellular system (haploid yeast). (Author abstract) (53 Refs)

63. HEPATIC MICROSOMAL METABOLISM AND MACROMOLECULAR BINDING OF THE ANTIOXIDANT, N-PHENYL-2-NAPHTHYLAMINE.

Anderson MM, Mitchum RK, Beland FA
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Xenobiotica; 12(1):31-43 1982

The hepatic microsomal metabolism of N-phenyl-2-naphthylamine (P2NA), an industrial antioxidant and suspected carcinogen, was studied in seven mammalian species to determine if N-dephenylation, reported to occur in vivo, could be demonstrated in vitro and if macromolecular binding occurs without an obligatory N-dephenylation. The rate of hepatic microsomal metabolism decreased in the order: hamster very much greater than mouse, greater than rat, approx equal to monkey, approx equal to dog, greater than human, approx equal to pig. Metabolism was increased by pretreatment with 3-methylcholanthrene or phenobarbital and decreased by carbon monoxide or 2-[(2,4-dichloro-6-phenyl)phenoxy]-ethylamine, which indicated the involvement of cytochrome P-450 rather than the flavoprotein mixed-function oxidase. All seven species produced two major metabolites identified as 6-hydroxy-P2NA and 4'-hydroxy-P2NA. The carcinogen 2-naphthylamine was not detected in the microsomal incubations. Incubations in the presence of 18O2 indicated that the oxygen incorporated in the products came from molecular oxygen. There was a time-dependent linear increase in covalent binding of P2NA to microsomal protein and the extent of binding approx paralleled the rate of metabolism. Thus, macromolecular binding of this aromatic amine appears to occur without an obligatory N-dephenylation and may be due to the metabolic formation of epoxides. (Author abstract) (31 Refs)

64. MUTAGENIC EVALUATION OF MORPHINE SULPHATE AND PETHIDINE HYDROCHLORIDE IN MICE BY THE MICRONUCLEUS TEST.

Das RK, Swain N
Sch. Life Sciences, Sambalpur Univ., Burla 768017, India
Indian J Med Res; 75:112-117 1982

Mutagenicity of morphine sulfate (MS) and pethidine hydrochloride (PH) was evaluated in vivo by the micronucleus test in mice. The animals were treated ip with various doses of either MS or PH twice with an interval of 24 hr. At 6 hr after the second treatment they were killed and bone marrow smears were prepared. Polychromatic and normochromatic erythrocytes and nucleated cells were examined for the occurrence of micronuclei. Distilled water treated individuals served the purpose of control. The erythrocytes showed significant increase in the incidence of micronuclei at all the dose levels tested for both the drugs, which clearly indicated chromosome breaking ability of the narcotics. Comparative analysis of the data for the two drugs exhibited slightly higher effectiveness of morphine in producing micronuclei. Importance was not attached to the incidence of micronuclei in the nucleated cells because of some doubt in scoring. The chromosome breaking activity of the narcotics and their probable modes of action have been discussed. (Author abstract) (21 Refs)

65. COMPARISON OF ENHANCEMENT OF GGTASE-POSITIVE FOCI AND INDUCTION OF ORNITHINE DECARBOXYLASE IN RAT LIVER BY BARBITURATES.

Pereira MA, Savage RE, Herren SL, Guion CW
Health Effects Res. Lab., United States Environmental Protection Agency, 26 West St. Clair St., Cincinnati, OH, 45268
Carcinogenesis; 3(2):147-150 1982

The induction of ornithine decarboxylase (ODC) by barbiturates and the ability of barbiturates to enhance neoplastic progression of chemically initiated cancer was examined in rat liver. All seven barbiturates induced ODC with barbital (7.7 fold increase) and phenobarbital (5.7 fold increase) demonstrating the most potent activity. Maximum induction of ODC by phenobarbital was obtained in 18 h, Barbital (500-5,000 ppm) and phenobarbital (500 ppm) administered in the drinking water enhanced the appearance of diethylnitrosamine (DENA)-initiated gamma-glutamyltranspeptidase (GGTase)-positive foci. Amobarbital, hexabarbital and pentobarbital did not enhance the appearance of GGTase-positive foci. In the absence of previous initiation by DENA, the enhancing regimen of the barbiturates did not cause the appearance of GGTase-positive foci. Barbiturates induced ODC activity in rat liver and enhanced the incidence of DENA initiated GGTase-positive foci. (Author abstract) (24 Refs)

66. PUVA: GAMBLING WITH A SYSTEM.

Strauss GH
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Int J Dermatol; 21(3):136-137 1982

Evidence for the pseudo-promoter (permissive carcinogen) status of psoralen-ultraviolet A (PUVA) is reviewed in regard to treatment of psoriasis. Xeroderma pigmentosum patients treated with PUVA have developed multiple cutaneous neoplasms within 1 mo. Other patients at risk for skin cancer have developed it less than 3 yr after PUVA therapy. Because PUVA suppresses delayed cellular hypersensitivity (DCH), patients undergoing PUVA therapy, particularly those with light skin getting intensive treatment, should be monitored for DCH response to dinitrochlorobenzene. (8 Refs)

67. FUNCTIONAL HETEROGENEITY OF UDP-GLUCURONOSYLTRANSFERASE ACTIVITIES IN C57BL/6 AND DBA/2 MICE.

Bock KW, Lilienblum W, Pfeil H
Dept. Pharmacology and Toxicology, Univ. Gottingen, Kreuzbergring 57, D-3400 Gottingen, W. Germany
Biochem Pharmacol; 31(7):1273-1277 1982

Functional heterogeneity of liver microsomal UDP-glucuronosyltransferase activities towards 1-naphthol, 4-methylumbelliferone or 3-hydroxybenzo(a)pyrene (UDP-GT1 activities) and morphine or 4-hydroxybiphenyl (UDP-GT activities) was studied in two inbred strains of mice which are genetically responsive (C57BL/6) or non-responsive (DBA/2) to methylcholanthrene-induction of drug metabolizing enzymes. 3-Methylcholanthrene preferentially induced UDP-GT1 activities in C57BL/6 mice. Phenobarbital, however, at low doses (50 mg/kg), selectively inhibited UDP-GT2 activities. Higher doses of phenobarbital (80 mg/kg) induced both UDP-GT1 and UDP-GT2 activities. In DBA/2 mice 3-methylcholanthrene-induction of UDP-glucuronosyltransferase activities was not detectable whereas enzyme induction by phenobarbital appeared to be unimpaired. UDP-GT1 activities were ubiquitously detectable in mouse tissues whereas appreciable UDP-GT2 activities were only found in liver and small intestinal mucosa. UDP-

GT1 (1-naphthol as substrate) was not inhibited by morphine suggesting different active sites for the conjugation of these substrates. The results suggest the presence of at least two functionally different forms of UDP-glucuronosyltransferase in mice. In conjunction with the results of Owens it is evident that one of these enzyme forms is regulated by the Ah locus. (Author abstract) (38 Refs)

68. GENETIC EFFECTS OF SOME PLATINUM CO-ORDINATION COMPLEXES ON E. COLI DNA AS REVEALED BY TRANSFORMATION STUDIES.

Hoekstra WP, Daemen CA, Otto ER
Dept. Molecular Cell Biology, State Univ. Utrecht, Padualaan 8, Utrecht 3584 CH, The Netherlands
Mutat Res; 94(1):53-62 1982

The genetic effects on Escherichia coli DNA of cis-diamminedichloroplatinum(II) (cisPt2), of its trans-isomer trans-PT2, and of cis-Pt(2.2-dimethyl-1,3-diaminopropane)Cl4 (cisPt4) are reported. Genetic analysis of transformants obtained with DNA treated by the various platinum complexes indicated that DNA lesions induced by cisPt2 and cisPt4 markedly influence genetic processing in recipient cells. No genetic effects were observed when trans-Pt2 was applied in similar concentrations. CisPt2 lesions appear to provide a stimulus for crossover events, while cisPt4 lesions lead to loss of linkage of genetic information in the donor DNA. The genetic effects of cisPt2 lesions in DNA were more pronounced in a uvrB recipient mutant than in a wild-type recipient, indicating that there is uptake of Pt-DNA and partial repair of Pt-induced lesions by the cellular excision repair system. The observation that transPt2 showed no effect when applied in similar concentrations at which cisPt2 gave significant effects may have relevance in terms of their differing efficacies as anti-neoplastic agents. (26 Refs)

69. INFLUENCE OF TEMPERATURE ON PLATINUM BINDING OF DNA, CELL KILLING, AND MUTATION INDUCTION IN ESCHERICHIA COLI K-12 CELLS TREATED WITH CIS-DIAMMINEDICHLOROPLATINUM(II).

Brouwer J, Fichtinger-Schepman AM, Van de Putte P, Reedijk J
Lab. Molecular Genetics, Wassenaarseweg 64, 2333 AL Leiden, The Netherlands
Cancer Res; 42(6):2416-2419 1982

Cell killing and specificity of mutation induction by treatment of Escherichia coli K-12 cells with cis-Pt(NH3)2Cl2 at various temperatures have been studied. Survival experiments show that the cell killing by cis-Pt(NH3)2Cl2 is enhanced with increasing temperature. This effect is explained by an increase in the amount of platinum bound to the DNA. The binding is the same in repair-proficient and in repair-deficient cells. However, the mutation induction in the lacl gene is much more strongly enhanced than could be expected from the increased platinum binding. This phenomenon is attributed to a different distribution of the induced lesions by cis-Pt(NH3)2Cl2 at various temperatures and not to an aberrant excision repair. Analysis of the induced lacl mutants revealed an increase in the percentage of nonsense mutants at higher temperature. Among the nonsense mutations, base-pair substitutions at GAG and particularly at GCG sequences are enhanced by the increasing temperature. The results are in agreement with our hypothesis that local denaturation of DNA, known to be promoted at higher temperature, is necessary for the formation of intrastrand cross-links at two guanine bases separated by a third base. (Author abstract) (10 Refs)

70. DISTRIBUTION OF THE LIVER CARCINOGEN METHAPYRILENE IN FISCHER RATS AND ITS INTERACTION WITH MACROMOLECULES.

Lijinsky W, Muschik GM
Chemical Carcinogenesis Program, Frederick Cancer Res. Center, P.O. Box B, Frederick, MD, 21701
J Cancer Res Clin Oncol; 103(1):69-73 1982

The anti-histaminic drug methapyrilene hydrochloride, which induces liver tumors in rats, was labeled with tritium by exchange and administered at a dose of 21 mg containing 700 uCi to each of 15 male Fischer rats. At 1 h, 6 h, 14 h, 24 h, and 44 h after treatment three rats were killed and their livers, pancreas, kidneys, and lungs were removed. The pooled organs were homogenized and DNA, RNA, and soluble protein were isolated from each. The extent of interaction of radioactive methapyrilene with liver nucleic acids was exceedingly small and did not differ significantly from the binding to nucleic acids in kidney, lung, or pancreas, which are not target organs of this carcinogen in rats. Binding of radioactivity to soluble proteins of the liver was considerable and substantially greater than in the other organs. If the mechanisms of carcinogenic action of methapyrilene involves covalent interaction with DNA this must be at a very low and highly specific level. (Author abstract) (4 Refs)

71. QUANTITATIVE STUDIES ON BLEOMYCIN-INDUCED STRAND BREAKAGE OF CHROMATIN DNA.

Kataoka K
Dept. Biochemistry, Cancer Inst., Okayama Univ. Medical Sch., Okayama 700, Japan
Okayama Igakkai Zasshi; 93(3/4):361-381 1981

Single and double strand breakage of DNA by bleomycin under various conditions was analyzed quantitatively using purified simian virus 40 (SV40) DNA and SV40 chromatin. The method employed for DNA assay was fluorometry of SV40 DNA separated into three forms I, II, and III by 1.4% agarose gel electrophoresis and stained with ethidium bromide. This method was extremely simple and accurate for quantitative estimation of single and double strand breakage of circular DNA. The amount of bleomycin required for in vitro breakage of SV40 chromatin DNA was much higher than that of naked SV40 DNA. 2-Mercaptoethanol accelerated bleomycin-induced DNA strand breakage. The concentration of 2-mercaptoethanol required for the acceleration was higher in SV40 chromatin than in SV40 DNA. DNA strand breakage was induced by ferrous ions in the absence of bleomycin to a similar level in SV40 chromatin and in SV40 DNA. The acceleration of bleomycin-induced strand breakage by a low concentration of ferrous ion was higher in SV40 DNA than in SV40 chromatin. Ethylenediamine tetraacetic acid (EDTA) and copper ions were not efficient for stopping the reaction of bleomycin-induced DNA breakage. Sodium dodecyl sulfate (SDS) was a useful reagent for stopping the reaction. (Author abstract) (75 Refs) (In JPN)

72. ANAPHASE ABERRATIONS: A MEASURE OF GENOTOXICITY IN MUTAGEN-TREATED FISH CELLS.

Kocan RM, Landolt ML, Sabo KM
Dept. Pathology, SM-30, Univ. Washington, Seattle, WA, 98195
Environ Mutagen; 4(2):181-189 1982

A continuous culture line of rainbow trout gonad (RTG-2) cells was exposed to benzo(a)pyrene (BAP), 3-methylcholanthrene (3MC), anthracene, 1-naphthol, 9-aminoacridine (9AA), mitomycin C (mit-C), and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). During exposure cells were examined for the presence of abnormalities in chromosome arrangement of anaphase figures during mitosis, and were compared to the effects of only solvent (dimethylsulfoxide). Both BAP and 3MC elevated the number of anaphase abnormalities, with more effect at 48 hr than at 24 hr. MNNG, mit-C, and 9AA were also effective in increasing the number of abnormalities. Abnormalities included mainly attached fragments, acentric fragments and bridges, with some side-arm bridges and multipolar cells. Toxicity and inhibition of cell division were also observed with all compounds. No increase in chromosomal lesions was observed in cells treated with naphthol or anthracene, suggesting that each chemical's characteristics, not the chemical class to which it belongs, are important in mutation induction. The in vitro RTG-2 cell system has a highly active mixed function oxygenase system, which eliminates the need for microsomal supplement. This test system is comparable to the Ames test and the sister-chromatid exchange test in sensitivity for measuring chromosome damage. (38 Refs)

73. INDUCTION OF SISTER CHROMATID EXCHANGES AND INHIBITION OF CELLULAR PROLIFERATION IN VITRO. I. CAFFEINE.

Guglielmi GE, Vogt TF, Tice RR
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Environ Mutagen; 4(2):191-200 1982

The ability of caffeine to induce sister-chromatid exchanges (SCEs) and to inhibit cellular proliferation of human lymphocytes in vitro was examined. Caffeine (0.10-4.10 milli(m)M) inhibited cellular proliferation in phytohemagglutinin-stimulated lymphocytes exposed continuously, but not in those receiving an acute 4-hr exposure. Administration of caffeine throughout the culture period induced a significant dose-dependent increase in SCEs, but exposure for 4 hr prior to the DNA synthetic period did not change SCE frequency. Using a linear regression curve derived from least squares analysis of the semilogarithmic plot of rate of SCE induction, the caffeine concentration capable of doubling the control SCE frequency was calculated as 2.4 mM. SCE induction rate in each of three bromodeoxyuridine replication cycles was the same. The mechanism for the results reported here is probably inhibition of DNA synthesis. Inhibition of DNA synthesis by caffeine may involve purine metabolism, transport, and salvage utilization in a direct or an indirect manner. The non-linearity of the SCE dose response curve for caffeine is in contrast to the typical linear graph for other well-known mutagenic/carcinogenic agents, suggesting that there is more than one mechanism of SCE induction. (52 Refs)

74. MUTAGENICITY OF DIBROMODULCITOL (DBD, AN ALKYLATING ANTICANCER DRUG) AND ITS MONO- AND BIFUNCTIONAL CONVERSION PRODUCTS STUDIED BY THE SALMONELLA/MICROSOME ASSAY.

Toth K, Sugar J, Somfai-Relle S, Hedegus L
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Carcinogenesis; 3(3):333-336 1982

Dibromodulcitol (DBD) and one of its most important bifunctional transformation products, dianhydrogalactitol (DAG) with similar cytostatic effect, were tested by the Salmonella/microsome assay on strains TA1535, TA1538, TA98 and TA100 using the plate incorporation technique. Both drugs were direct mutagens in strains TA1535 and TA100 and nonmutagenic in other strains. Their mutagenic effect was not influenced by S-9 mix from rat liver. Mutagenicity of DAG was very limited because of its marked toxicity. The other monofunctional alkylating derivatives, ie, 1-bromo-3,6-anhydrodulcitol and 1,2-epoxy-3,6-anhydrodulcitol were highly mutagenic in strains TA1535 and TA100 with and without S-9 mix despite having no anticancer effect. Anticancer activity was exerted only by the bifunctional alkylating hexitols (DBD, DAG) which showed moderate mutagenic activity compared to the monofunctional derivatives. No correlation could be established between the mutagenic and anticancer effect of the four structurally related hexitols. Mutagenicity of urine and bile from rats after a single administration of the max tolerated (450 mg/kg) dose of DBD was also examined, and the hexitol components of the same urine sample were identified by the DBD and its mutagenic transformation products were excreted in urine and not through the bile. The mutagenic effect of DBD observed cannot be attributed exclusively to DBD itself, because the parent molecule, like other alkylating agents, easily undergoes spontaneous decomposition under in vitro and in vivo conditions to release both bi- and monofunctional alkylating solvolysis products and these highly reactive derivatives may play a role in this effect. No significant difference in the relative mutagenicity was detected between DBD and cyclophosphamide, used as a reference substance. (Author abstract) (38 Refs)

75. INDUCED CHROMOSOME LOSS FOLLOWING TREATMENT OF POSTMEIOTIC CELLS OF THE DROSOPHILA MELANOGASTER MALE WITH MMS AND DMN AND MATINGS WITH REPAIR-PROFICIENT FEMALES AND REPAIR-DEFICIENT FEMALE MEI-9A AND ST MUS302.

Zimmering S
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Mutat Res; 94(1):79-86 1982

Frequencies of complete and partial loss of the Y chromosome in Drosophila melanogaster ring-X males treated with methylmethanesulfonates (MMS) or dimethylnitrosamine (DMN) and mated with repair-proficient females or the repair-deficient females, mei-9a and st mus302, are reported. When males were treated with MMS and mated with the repair-deficient females, significant enhancement of induced complete loss (CL) and partial loss (PL) above controls was observed. Frequencies of induced loss were 10x higher with st mus302 than mei-9a. The same trends were observed with DMN. It was observed that st mus302 females were equally sensitive to MMS and DMN-induced break/pre-break lesions, while mei-9a females were less sensitive to MMS- than to DMN-induced lesions. Of 37 PLs observed in the mei-91 series, 13 were mosaics; of 50 with st mus 302, only one was a mosaic. The same phenomenon was observed for procarbazine and diethylnitrosamine (DEN). St mus302 females were more sensitive than mei-9a females and markedly more sensitive than repair-proficient females regarding the recovery of CLs and PLs in tests of procarbazine, DEN, MMS and DMN. Frequencies of chromosome loss are substantially higher with MMS and DMN than procarbazine and DEN. (6 Refs)

76. TOXICITY AND METABOLISM OF ACRYLONITRILE.

Sapota A, Chmielnicka J
Zaklad Metabolizmu Substancji Toksycznych, Instytut Medycyny Pracy, ul. Teresy 8, 90-950 Lodz, Poland
Med Pr; 32(1):25-33 1981

Studies in experimental animals and in vitro culture on the toxic effects and metabolism of acrylonitrile (AN) are reviewed. AN was found to be mutagenic for certain strains of Salmonella typhimurium and Escherichia coli. Increased incidence of tumors of the mammary glands, stomach, peripheral nervous system and sebaceous glands of the auditory meatus was found in female rats inhaling AN for 52 wk compared with controls. (40 Refs) (In POL)

77. DRUG-INDUCED ALTERATIONS OF THE LIVER. HISTOLOGICAL ASPECTS.

Desmet VJ
Pathologische ontleedkunde II, Academisch Ziekenhuis Sint-Rafael, B-3000 Leuven, Belgium
Acta Gastroenterol Belg; 44(9/10):367-374 1981

Histological characteristics of drug-induced liver disorders are described. Administration of methotrexate for psoriasis may result in hypertrophy and proliferation of liver fibroblasts. Liver irradiation and urethane exposure can cause obliteration of centrolobular veins. Liver adenoma, focal nodular hyperplasia, and hepatocellular carcinoma have been related to the chronic use of oral contraceptives. Exposure to vinyl chloride and ingestion of arsenic compounds has been related to the development of liver angiosarcoma. The differential diagnosis of cholestasis and other disorders, including Hodgkin's and non-Hodgkin's lymphomas is discussed. (8 Refs) (In FRE)

REVIEWS AND OTHER COMPOUNDS

78. IMPORTANT NEW FINDINGS ON PASSIVE SMOKING.

Schmidt F
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Oeff Gesundheitswes; 44(2):130-132 1982

Five arguments for defining passive smoking as a true health risk, rather than merely an annoyance, are presented. Tobacco smoke contains greater than 40 carcinogenic substances. Most of these substances are not inhaled by the active smoker alone. Carcinogenicity of the substances has been confirmed in animal studies. Carcinogens in smoke show a summation effect without evidence of a threshold effect. Recent studies are cited to support arguments for imposition of legal restrictions on smoking in public. (35 Refs) (In GER)

79. SCE AND UDS STUDIES IN A FAMILY WITH RETINOBLASTOMA: A CASE STUDY.

Fabricant JD, Au W, Fabricant RN, Morgan KS
Dept. Preventive Medicine and Community Health, Div. Genetic Toxicology, Univ. Texas medical Branch, Galveston, TX
Teratogenesis Carcinog Mutagen; 2(1):85-90 1982

Lymphocytes from a father and daughter with retinoblastoma were analyzed for spontaneous and mitomycin C (MMC)-induced sister chromatid exchanges (SCE) and unscheduled DNA synthesis (UDS) induced by MMC and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), compared to results from two controls. Cells for the SCE studies were treated with 10(-8) and 10(-7) M MMC, and those for the UDS studies with 0.3-10 ug/ml MMC or 1-30 x ug/ml MNNG. SCE were identified after staining by the fluorescent-plus Giemsa technique, and UDS by incorporation of 3H-thymidine. Spontaneous and induced SCE frequencies were similar in retinoblastoma and control lymphocytes. UDS was the same for both groups after MMC treatment, but was not increased in the experimental group after MNNG treatment, as compared to an increase seen in the control group. Results indicate that lymphocytes from retinoblastoma patients respond normally to the cross-linking agent MMC, but are unable to repair DNA damage caused by the alkylating agent MNNG. (18 Refs)

80. CLONED TRUNCATED RECA GENES IN E. COLI. I. EFFECT ON RADIOSENSITIVITY AND RECA+ DEPENDENT PROCESSES.

Sedgwick SG, Yarranton GT
Genetics Div., Natl. Inst. Medical Res., London NW7 1AA, England
MGG; 185(1):93-98 1982

Plasmids pMH1 and pDR1461, possessing the control region and 22% or 73% of the Escherichia coli recA gene, conferred UV sensitivity to wild-type uvrA, and umuC bacteria. Sensitization was less in recA441 (tif-1) mutants and absent in lexA cells. Radiosensitization correlated with inhibition of recombinational repair, even through induced recA protein synthesis and recombination in Hfr matings were normal. Plasmids pMH1 and pDR1461 also prevented induction of some, but not all, SOS functions. Mutagenic reversion to tryptophan prototrophy and induced reactivation of UV-irradiated phage lambda were eliminated, and the efficiency of lambda lysogenic induction reduced. However, naladixic acid induced filamentous growth, mitomycin-C induced uvrA gene expression and post UV-irradiation DNA degradation control were little changed. Explanations of these effects are discussed which involve the presence of either truncated recA protein or multiple copies of the recA gene control sequence. (Author abstract) (41 Refs)

81. DETERMINATION OF MUTAGENIC POTENTIAL AND ORGANIC CONTAMINANTS OF GREAT LAKES DRINKING WATER.

Williams DT, Nestmann ER, LeBel GL, Benoit FM, Otson R
Bureau Chemical Hazards Environmental Health Directorate, Dept. Natl. Health and Welfare, Ottawa K1A OL2, Canada
Chemosphere; 11(3):263-276 1982

Summer and winter water samples taken directly from 12 treatment plants were passed through ion exchange resin filters to extract organic contaminants. Winter grab samples of raw and treated water were also taken at each plant at the same time and analyzed for volatile organics. The resin extracts were tested for mutagenicity with/without S9 activation against Salmonella typhimurium TA98 and TA100. The extracts were also analyzed for organochlorine and organophosphorus pesticides (OPP), trialkylphosphates and triarylphosphates (TAP), polychlorinated biphenyl (PCB), and polycyclic aromatic hydrocarbons (PAH). Extracts taken to dryness were more mutagenic than those left in solution. Mutagenicity was higher in the summer samples (11/12) than winter samples (7/12). Aggregate PAH was higher (11/12) in winter samples however; naphthalene, biphenyl, dibenzyl, fluorene, anthracene or phenanthrene, fluoroanthrene, pyrene, stilbene, fluorenone, and anthraquinone were found. The extracts contained (a) alpha-BHC and beta-BHC, both generally higher in winter, (b) no PCB or OPP, (c) TAP: ethyl, n-butyl, 2-chloroethyl, 1,3-dichloropropyl, butoxyethyl, phenyl, and cresyl, in seven instances only in summer samples. The grab samples contained bromodichloromethane, chlorodibromomethane, chloroform, toluene, m-xylene, and o-xylene. No relationships between relative mutagenicity and identified contaminants could be deduced. (19 Refs)

82. CARCINOGENIC EFFECT OF RADIOACTIVE PRODUCTS.

Vasilenko IIa
No affiliation given
Vopr Onkol; 28(1):76-83 1982

Clinical and experimental data on the carcinogenic effects of the products of nuclear fission (PNF) are reviewed. The incidence and spectrum of PNF-induced tumors depended upon the radiation dosage, the age of the animal, and the nature of PNF. Exposure to chemical carcinogens was shown to enhance the incidence of PNF-induced neoplasms. Administration of thyrostatic agents provided protection against carcinogenic effects of iodine radioisotopes. (32 Refs) (In RUS)

83. CERTAIN ASPECTS OF LUNG CANCER PROPHYLAXIS AND MANAGEMENT.

Napalkov NP, Barchuk AS, Merabishvili VM
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Vestn Khir; 128(1):20-25 1982

Lung cancer morbidity indices in the Soviet Union are reviewed with special emphasis on the role of smoking and environment carcinogens in the etiology of the lung cancer. Prophylaxis of the occupational lung cancer includes prevention of the exposure to carcinogens, establishment of the max permissible levels of carcinogens, active campaign against smoking, and improvement of the methods of follow-up of the patients with precancerous conditions. It was recommended that the high risk group should include the patients with chronic pneumonia, pneumosclerosis, and chronic tuberculosis, as well as men and women greater than 50 yr with prolonged history of smoking. Unsatisfactory results of the treatment (only 30.6% of the patients in Stage II underwent surgery in combination with chemotherapy or radiotherapy) are associated with insufficient oncological awareness of general practitioners and thus with the delayed diagnosis. (4 Refs) (In RUS)

84. RADIATION EQUIVALENCE OF GENOTOXIC CHEMICALS. VALIDATION IN CULTURED MAMMALIAN CELL LINES.

Murthy MS
Div. Radiological Protection, Bhabha Atomic Res. Center, Trombay, Bombay-400 085, India
Mutat Res; 94(1):189-197 1982

Radiation-equivalent chemical (REC) values were computed for the monofunctional alkylating agents ethylmethanesulfonate (EMS), methylmethanesulfonate (MMS), N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG), N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), ethylnitrosurea (ENU), and methylnitrosourea (MNU). REC values were calculated from published data as the ratio of the mutation frequency per unit dose of ionizing radiation to that of the alkylating agent. Mutation frequency data from different sources for a given cell line and locus were pooled and the mean taken. REC values were found to decrease in the order: nitrosoguanidine greater than nitrosourea greater than methylsulphonic esters. REC values for methylating agents were less than for corresponding ethylating agents. REC values for a given alkylating agent were not dependent upon cell line or locus, and fell within a narrow range for the rodent cell lines considered. Mutation frequency was expressed as the number of induced mutations/survivor/unit dose; for chemicals the unit was molar x hr (Mh). These values for the alkylating agents were: 1.28-5.49 x 10(-6) Mh for EMS; 3.57-14.30 x 10(-7) Mh for MMS; 2.60-3.90 x 10(-8) Mh for ENU; 7.50-17.81 x 10(-9) Mh for MNU; 7.36-13.89 x 10(-10) Mh for ENNG; and 4.27-32.50 x 10(-11) Mh for MNNG. These results validate the REC concept in mammalian cells, including human cells. (37 Refs)

85. MUTAGENS, CARCINOGENS, AND TUMOR PROMOTERS IN OUR DAILY FOOD.

Sugimura T
Natl. Cancer Res. Inst., Tsukiji, Chuo-ku, Tokyo, Japan
Cancer; 49(10):1970-1984 1982

Identification of mutagens, carcinogens, tumor promoters in human food is reviewed. Studies of the food additive 2-(2-furyl)-3-(5-nitrofuryl)acrylamide, which is mutagenic in the Ames test and produced tumors in mice, indicated that if a compound in food shows mutagenicity, its carcinogenicity should be considered and that data obtained on mutagenicity prior to 1960 may be invalid. Improvement and adoption of the Ames test for screening for carcinogens in food are discussed. Isolation and identification of new heterocyclic amines from pyrolysates of amino acids, proteins, and proteinous foods are described. Mutagens and carcinogens in edible plants, vegetables, fruits, alcoholic spirits, spices, and beverages are described. Tumor promoters are discussed in relation to life style. Recommendations are proposed for cancer prevention. (159 Refs)

86. DIFFERENT PATTERNS OF BENZO[A]PYRENE METABOLISM OF PURIFIED CYTOCHROMES P-450 FROM METHYLCHOLANTHRENE, BETA-NAPHTHOFLAVONE AND PHENOBARBITAL TREATED RATS.

Gozukara EM, Guengerich FP, Miller H, Gelboin HV
(c/o Gelboin) Lab. Molecular Carcinogenesis, NCI, NIH, Bethesda, MD, 20205
Carcinogenesis; 3(2):129-133 1982

An improved high-pressure liquid chromatography system was used to analyze the amount of benzo[a]pyrene metabolites formed in reconstituted microsomal mixed-function oxidase systems containing different cytochromes P-450. We separated 12 identified and 7 unknown metabolites of BP which included 3 diols: the 9,10-, 4,5-, and 7,8-dihydrodiols; 4 phenols, 9-, 7-, 1-, and 3-hydroxybenzo[a]pyrene (OH-BP); and 3 quinones: the 1,6-, 3,6-, and 6,12-quinones. Two additional peaks co-migrated with synthetic 4-OH-BP and 5-OH-BP, respectively. The former, designated fraction 1, was shown by uv spectra to contain primarily the 4,5-epoxide with small amounts of 4-OH-BP. The total metabolism of BP was found to be approx 20-fold greater with the cytochrome P-450 from the 3-methylcholanthrene (P-450 3-MC) and beta-naphthoflavone (P-450 BNF) treated rats than with the phenobarbital preinduced cytochrome P-450 (P-450 PB). 3-OH-BP and 9-OH-BP were the major phenolic products for both P-450 3-MC and P-450 BNF whereas the 3-OH-BP and 1-OH-BP were the major phenolic products for P-450 PB. The ratio of total phenols to diols was found to be 3.34, 4.85 and 0.70 for P-450 3-MC, P-450 BNF and P-450 PB. The major dihydrodiol generated by P-450 3-MC and P-450 BNF was 7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene, whereas the 9,10-diol was the major diol from P-450 PB. The amount of 1,6-and 3,6-quinones produced was greater than the 6,12-quinone with the P-450 3-MC and P-450 BNF but all three quinones were produced in low and equal amounts by the P-450 PB. In respect to the percent metabolites formed at a given region of the BP, P-450 3-MC and P-450 BNF preferred oxidation at the 1, 3 positions, 6 position and the 7, 8 positions, whereas the P-450 PB preferred oxidation at the 4, 5 position.

This study demonstrates the unique positional specificity of different forms of cytochrome P-450 which may regulate the balance between activation and detoxification pathways of polycyclic aromatic hydrocarbon metabolism. (Author abstract) (28 Refs)

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1. TOXICITY AND METABOLISM OF ACRYLONITRILE.
Sapota A, Chmielnicka J
Zaklad Metabolizmu Substancji Toksycznych, Instytut Medycyny Pracy, ul. Teresy 8, 90-950 Lodz, Poland
Med Pr; 32(1):25-33 1981
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2. A REVIEW OF THE GENOTOXICITY OF FOOD, DRUG AND COSMETIC COLOURS AND OTHER AZO, TRIPHENYLMETHANE AND XANTHENE DYES.
Combes RD, Haveland-Smith RB
Dept. Biological Sciences, Portsmouth Polytechnic, King Henry I St., Portsmouth, PO1 2DY, Hants, England
Mutat Res; 98(2):101-248 1982

3. CARCINOGENICITY OF AIRBORNE FINE PARTICULATE BENZO(A)PYRENE: AN APPRAISAL OF THE EVIDENCE AND THE NEED FOR CONTROL.
Perera F
Natl. Resources Defense Council, Inc., 122 East 42nd St., New York, NY, 10168
Environ Health Perspect; 42:163-185 1981

4. TOXICOLOGY OF N-NITROSO COMPOUNDS.
Coulston F, Olajos EJ
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5. CRITICAL REVIEW OF THE MUTAGENIC AND OTHER GENOTOXIC EFFECTS OF DIRECT COAL LIQUEFACTION.
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Critical Review of the Mutagenic and Other Genotoxic Effects of Direct Coal Liquefaction. Available from National Technical Information Service, Springfield, VA, as DE81027859:, 216 pp., 1981.

6. CARCINOGENICITY AND ITS EFFECT ON MEDICINAL RESEARCH PROGRAMS IN THE USA.
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Med Res Rev; 2(2):153-166 1982

7. ANTIPROTOZOAL DRUGS (SIDE EFFECTS).
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Side Eff Drugs Annu; (5):278-284 1981

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10. NEPTUNIUM - THE NEGLECTED ACTINIDE: A REVIEW OF THE BIOLOGICAL AND ENVIRONMENTAL LITERATURE.
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No affiliation given
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DIETARY FACTORS IN CARCINOGENESIS

12. FIBRES, NUTRITION AND THE GUT.
Schrijver M, Tytgat GN
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14. ASSESSING HUMAN EPIDEMIOLOGIC DATA ON DIET AS AN ETIOLOGIC FACTOR IN CANCER DEVELOPMENT.
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17. SKIN CANCER: OCCUPATIONAL CAUSES.
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18. OCCUPATIONAL AND ENVIRONMENTAL HEALTH PROBLEMS OF THE DEVELOPING OIL SHALE INDUSTRY: A REVIEW.
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21. OSHA AT THE THRESHOLD: SETTING PERMISSIBLE EXPOSURE LEVELS FOR KNOWN CARCINOGENS AFTER AMERICAN PETROLEUM INSTITUTE.
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25. TUMOR PROMOTION BY REGENERATIVE EPIDERMAL HYPERPLASIA IN MOUSE SKIN.
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27. UTILIZATION OF CELL TRANSFORMATION TESTS IN THE DETECTION OF CHEMICAL CARCINOGENS.
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Cancer; 49(9):1739-1745 1982

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CHEMICAL CARCINOGENESIS

Miscellaneous Agents

SERIES CK13 No. 82/10

OCTOBER, 1982

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HYDRAZINES AND RELATED COMPOUNDS

1. MECHANISM OF ORGAN-SPECIFIC TUMOR INDUCTION IN THE GASTRO-INTESTINAL TRACT (MEETING ABSTRACT)

Kleihues P
Universitat Freiburg, Albertstrasse 19, D 7800 Freiburg, W. Germany
J Cancer Res Clin Oncol; 103(Suppl):A11 1982

The metabolism and reaction with DNA of three carcinogens was investigated after systemic administration selectively induced tumors in different segments of the gastro-intestinal tract. These agents share a common ultimate carcinogen, methyl diazonium ion, and produce an identical pattern of methylated DNA bases. Following oral or systemic administration in rats, N-nitrosomethylbenzylamine (MBN) induced a high incidence of esophageal carcinomas. Methylation of DNA purines by a single iv dose of (methyl-14C) MBN is most extensive in the esophagus, followed by liver, lung and forestomach. In mice, systemic application of MBN resulted in the development of forestomach carcinomas as in this species, DNA methylation by MBN is higher in forestomach than in esophageal DNA. The alternative possibility of enzymic hydroxyla-

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tion of the methyl group of MBN cannot be ruled out but after administration of (methylene-14C) MBN no benzylated DNA bases were detected in rat tissues. Methyl(acetoxymethyl)nitrosamine (DMN-OAc) is a stable derivative of the alpha-hydroxy intermediate of dimethylnitrosamine. Heterolytic decomposition of DMN-OAc occurs through esterase mediated cleavage of the acetoxy moiety. Following iv injection of (14C)DMN-OAc by far the highest levels of DNA alkylation were found in the lung, the principal target organ for this route of application. In contrast, ip injection of (14C) CMN-OAc resulted with a preferential alkylation of organs bordering the abdominal cavity with highest values in ileum and colon, the target organs for this route of application. Weekly sc injection of 1,2-dimethylhydrazine (DMH) in rats and mice cause a selective induction of colon carcinomas. Alkylation of DNA purines by DMH was highest in liver, followed by colon, kidney and ileum. (no Refs)

2. CYTOLOGIC AND BIOCHEMICAL GENETIC EFFECTS OF CHEMICAL CARCINOGENS.

Rasmussen RE
Dept. Community and Environmental Medicine, California Univ., Irvine, CA
Cytologic and Biochemical Genetic Effects of Chemical Carcinogens. Available from National Technical Information Service, Springfield, VA, as AD-A107 615/7:, 43 pp., 1981.

The first project is concerned with the relationship between initiation of cancer by chemicals and the damage and repair of DNA in cells and tissues susceptible to the carcinogenic action of the chemicals. The working hypothesis is that interaction of the carcinogen with cellular DNA is a necessary step in carcinogenesis and that this interaction may cause DNA damage which is then followed by DNA repair synthesis. The second project was conducted with the cooperation of the staff of the Toxic Hazards Research Unit at AMRL, WPAFB. Rats and hamsters were exposed by inhalation to hydrazine at 750 ppm for 1 hr. Groups of animals which had been exposed only once or which had been exposed 10 times were shipped to UC Irvine for study. The factors studied were (1) DNA replication in the lung; (2) DNA repair synthesis in the lung; (3) Cellular replication in the lung and nasal turbinates; and (4) Metabolism of a known lung carcinogen, 3H-benzo(a)pyrene, by lung slices from the treated animals. The third project was initiated during the current year with the goal of developing an animal model in which biochemical and cytogenetic factors could be studied during the process of tumorigenesis. Range-finding studies are underway at the Toxic Hazards Research Unit to establish the intratracheal dosage of 3-methylcholanthrene necessary to produce a high yield of lung tumors in Fischer 344 rats within 12 months. (Author abstract)

3. COMPARATIVE BIOCHEMISTRY AND METABOLISM. PART I. CARCINOGENESIS.

Shank RC
Dept. Community and Environmental Medicine, California Univ., Irvine, CA
Comparative Biochemistry and Metabolism. Part I. Carcinogenesis. Available from National Technical Information Service, Springfield, VA, as AD-A107 614/0:, 38 pp., 1981.

Oral administration of the inorganic hepatotoxin, hydrazine, to male Fischer 344 or Sprague Dawley rats results in the endogenous methylation of liver DNA at the 7-and O6-positions of guanine. At doses below the LD50 (45, 60 or 75 mg hydrazine/kg body wt), methylation levels varied little and averaged about 500 micromol 7-methylguanine/mol guanine and 20 micromol O6-methylguanine/mol guanine. At 90 mg hydrazine/kg body wt (approx the 7-day LD50) the methylation levels were 869 micromol 7-methylguanine and 58 micromol O6-methylguanine/mol guanine 24 hr after toxicant administration. A single dose of 3 mg hydrazine/kg body wt did not result in detectable levels of methylguanine in liver DNA; however, after three or four daily administrations of hydrazine at this dose, liver damage was evident, and liver DNA contained 50-100 micromol 7-methylguanine/mol guanine, about the limit of analytical detection. Following a single oral administration of 90 mg hydrazine/kg body wt, liver DNA guanine rapidly became methylated. The time for half-maximum alkylation at 7-guanine was 30 minutes and at O6-guanine, 45 minutes. The rates of removal of these methylated bases were consistent with published values from experiments using methylating carcinogens and with values obtained in this laboratory with the model compound, 1,2-dimethylhydrazine. (Author abstract)

4. PATHOGENESIS OF 1,2-DIMETHYLHYDRAZINE-INDUCED CARCINOMAS IN RAT INTESTINE. 1. THE INDUCTION OF MUCIN PRODUCING CARCINOMAS IN RAT INTESTINE.

Takemiya M, Miyayama H, Takeuchi T
Dept. Pathology, Kumamoto Univ. Sch. Medicine, 2-2-1 Honjo, Kumamoto 860, Japan
Acta Pathol Jpn; 32(2):257-264 1982

Seventy four white male Wistar rats were divided into two groups and given weekly subcutaneous injections of 30 mg 1,2-dimethylhydrazine (DMH) 2HCl/kg body weight for 10 or 15 weeks, respectively, and the histological properties and distribution of DMH-induced rat carcinomas were investigated. The carcinomas induced by DMH were classified mainly into mucin producing carcinomas and non-mucin producing ones. In the large intestine, the group treated for 15 weeks induced significant incidences of mucin producing carcinomas composed mainly of cells containing intracellular mucin. Mucin producing carcinomas consisted of poorly differentiated adenocarcinoma, signet ring cell carcinoma and mucinous carcinoma, and these often coexisted within the same tumor mass. Mucin producing carcinomas tended to develop in the proximal colon and cecum, while non-mucin producing carcinomas were frequent in the distal colon. This method was thought to be a useful model to study glycoproteins of cancer cells. (Author abstract) (17 Refs)

5. EFFECT OF CHEMICAL MUTAGENS ON HERPES VIRUS-INDUCED CELLULAR TRANSFORMATION AND TESTING FOR MUTAGENESIS IN MOUSE CELLS.

Johnson FB
Dept. Microbiology, Brigham Young Univ., Provo, UT
Effect of Chemical Mutagens on Herpes Virus-induced Cellular Transformation and Testing for Mutagenesis in Mouse Cells. Available from National Technical Information Service, Springfield, VA, as AD-A102 854/7:, 17 pp., 1981.

The temperature sensitive (ts) mutant A8(293) of herpes simplex Type 2 virus (HSV-2) was employed in tests to detect chemical interactions with the virus causing increased transformation of target cells. Mouse 3T3 cells were monitored for morphological transformation. Hydrazine and 1,2-dimethylhydrazine caused an enhancement of viral transformation of between three to four fold, confirming earlier findings using ultraviolet light inactivated wild type virus. Norharman (9H-pyrido[3,4-b]indole), a component to tobacco tars, caused a nearly three-fold enhancement of transformation. Xylene and toluene were not found to enhance viral transformation. Experiments involving host-mediated activation of the test chemicals were unsuccessful because of low target cell recovery due to inhibition of the target 3T3 cells. (Author abstract)

6. CHEMICAL INTERACTIONS WITH HERPES SIMPLEX TYPE 2 VIRUS: ENHANCEMENT OF TRANSFORMATION BY HYDRAZINE AND 1,2-DIMETHYLHYDRAZINE.

Johnson FB
Dept. Microbiology, Brigham Young Univ., Provo, UT, 84602
Chem Biol Interact; 40(1):97-112 1982

Quantitative assays for the morphological transformation of 3T3 Swiss mouse cells by herpes simplex Type 2 virus (HSV-2) were employed to examine the effect on cell transformation of chemical carcinogens and suspected carcinogens. Exposure of the cells to the chemical compound, followed by virus infection, resulted in enhancement of transformation when compared to that observed with chemical or virus alone. Enhancement occurred in tests utilizing either UV light-inactivated HSV-2 (strain 333) or a temperature-sensitive (ts) mutant of HSV-2 [A8(293)]. A series of seven ts-mutants were tested and exhibited varying degrees of transformation. Enhancement of transformation occurred in cells treated with hydrazine (HZ) and 1,2-dimethylhydrazine (SDMH). No enhancement occurred when cells were treated with monomethylhydrazine, 1,1-dimethylhydrazine and the jet fuels JP-5, JP-10, RJ-4 and RJ-5. A strong time dependence after treatment was demonstrated with some enhancement seen at 6 hr after chemical treatment but the greatest enhancement appeared when virus infection began after 24 hr of chemical exposure. (Author abstract) (25 Refs)

7. EFFECT OF ESTRADIOL PROPIONATE AND PREGNANCY ON CARCINOGENESIS INDUCED BY 1,2-DIMETHYLHYDRAZINE IN C3HA MICE.

Turusov VS, Murovannyi AN, Morozova OV
All-Union Cancer Res. Center, Moscow, USSR
Eksp Onkol; 4(2):20-23 1982

The effects of pregnancy and estradiol propionate (EP) administration on 1,2-dimethyl hydrazine (DMH)-induced carcinogenesis were studied in female C3HA mice. Virgin or pregnant females were subjected to sc administrations of DMH (8 mg/kg/wk) alone or in combination with EP (10 ug/kg/wk). DMH and EP were given for 30 wk. Animals were followed up for 50 wk after the initiation of the experiment. DMH alone induced tumors in 75% of virgin mice and in 56.2% of pregnant mice. EP administration resulted in a marked increase of the incidence of colonic tumors (31.6%, compared with 8.3% after administration of DMH alone to virgin mice and 18.7% after administration of DMH alone to pregnant mice). Uterine sarcomas were observed in 28.9% of mice treated with DMH + EP, while all mice treated with DMH alone were free of uterine sarcomas. Hepatocellular tumors were observed only in mice treated with DMH + EP (23.7%). These findings indicate that EP can modify the DMH-induced carcinogenesis not only in the hormone dependent organs but also in the liver and in the colon. (14 Refs) (In RUS)

8. EXPERIMENTAL COLORECTAL CARCINOGENESIS.

Martin MS
Laboratoire d'Immunologie, Faculte de Medecine, 7, boulevard Janne-d'Arc, F-21033 Dijon, France
Gastroenterol Clin Biol; 6(4):382-391 1982

Multiple intestinal tumors have successfully been induced in rats following 6 mo of subcutaneous injection with 1,2-dimethylhydrazine (DMH). The specificity of DMH depends to a large extent on the mode of administration, and the dose modifies the distribution of the lesions. DHM induces more intestinal tumors at low doses than some of the other compounds used for carcinogenic purposes. Age of the animal has an effect on the specificity of the action of carcinogens. Sex of the animal is also a factor in intestinal carcinogenesis. Intestinal tumors induced by DMH appear more rapidly in males than in females who seem less susceptible to colorectal cancers. The most frequently induced tumors are adenocarcinomas which occurs most often in the distal half of the colon. Mucous secreting carcinomas which predominate in the proximal part of the colon are less commonly encountered. Adenomas are observed much more commonly in the mouse than in the rat and they resemble the human adenomas. Like human colon cancers, experimental cancers of the colon can produce more or less specific antigens. The morphological transformation of the colons epithelial cells is accompanied by biochemical alterations and complex interactions affecting nutrition, intestinal flora, biliary acids, and immune defenses. Animal models are necessary to study the complicated assortment of factors in human colon cancer. (107 Refs) (In FRE)

9. INTERFERENCE WITH DIMETHYLHYDRAZINE INDUCTION OF COLON TUMORS IN MICE BY EPSILON-AMINOCAPROIC ACID.

Corasanti JG, Hobika GH, Markus G
Dept. Experimental Biology, Roswell Park Memorial Inst., New York State Dept. Health, Buffalo, NY, 14263
Science; 216(4549):1020-1021 1982

The antifibrinolytic agent epsilon-aminocaproic acid given in the drinking water to Swiss ICR/Ha mice significantly counteracted the appearance of colorectal tumors induced by 21 weekly injections of 1,2-dimethylhydrazine. The drug affected both the number and the location of the tumors and, in some animals, altogether prevented their appearance. The low concentrations of epsilon-aminocaproic acid in the plasma of four control mice given the agent labeled with carbon-14 for 3 days suggest that the effect may depend not on inhibition of plasminogen activator activity, but on interference with the binding of some substance to the strong lysine binding site of plasminogen. (Author abstract) (29 Refs)

10. DIMETHYLHYDRAZINE-INDUCED COLONIC NEOPLASIA: DISSOCIATION FROM ENDOGENOUS GASTRIN LEVELS.

Oscarson JE, Veen HF, Ross JS, Malt RA
(c/o Malt) Massachusetts General Hosp., Boston, MA, 02114
Surgery; 91(5):525-530 1982

The potential tropic effect of gastrin in promoting colonic carcinogenesis was tested in rats (n = 133) with 6-to 16-fold variations in endogenous gastrin resulting from antrectomy or fundectomy, followed by 12 injections of 1,2-dimethylhydrazine (10 mg/kg). The incidence and grade of differentiation of resulting tumors, as well as the thickness, content of nucleic acids, and specific activity of DNA in colonic mucosa, were similar in both high-gastrin and low-gastrin animals and were unchanged from data in unoperated control animals receiving only the carcinogen. Long-term changes in endogenous gastrin concentration are not followed by colonic mucosal tropic effects, and gastrin does not act as a cofactor in dimethylhydrazine-induced carcinogenesis at this dosage. (Author abstract) (25 Refs)

11. DETECTION OF CARCINOGENIC EXPOSURES BY URINALYSIS: INDUCTION OF CELL-MEDIATED IMMUNITY.

Stevens RH, Cole DA

Radiation Res. Lab., Dept. Radiology, Univ. Iowa, Iowa City, IA, 52242

Toxicol Lett; 11(3/4):299-303 1982

The colon carcinogen 1,2,-dimethylhydrazine (DMH: 0.1 to greater than 10 mg/kg) was administered sc to male Fisher F344 inbred rats; urine was collected over a 24 hr period and injected ip into a group of normal unexposed rats. DMH and its metabolites were excreted within 15 min in the urine and nearly 65% metabolized over a 24-hr interval. Cell mediated immunity (CMI) was measured by killing/injury of cultured x-ray induced rat small bowel adenocarcinoma target cells by peripheral blood lymphoid cells of urine-exposed animals. CMI was increased by urine collected from DMH exposed rats; a dose-response curve relationship was found, suggesting the presence of mutagenic/carcinogenic components. Although the actual DMH concentration in the urine was not known, it was less than 10(-4) times LD50 (1 g/kg) and 10(-3) times the amount necessary for tumor induction over a 20-mo latency period. This method has potential as a rapid non-invasive technique for screening individuals exposed to carcinogens. (15 Refs)

12. PATHOGENESIS OF 1,2-DIMETHYLHYDRAZINE-INDUCED CARCINOMAS IN RAT INTESTINE. II. HISTOCHEMICAL AND ULTRASTRUCTURAL CHARACTERISTICS OF GLYCOPROTEINS OF 1,2-DIMETHYLHYDRAZINE-INDUCED CARCINOMA CELLS.

Takemiya M, Miyayama H, Takeuchi T

Second Dept. Pathology, Kumamoto Univ. Sch. Medicine, 2-2-1 Honjo, Kumamoto 860, Japan

Acta Pathol Jpn; 32(2):265-279 1982

Two hundred twenty seven lesions of DMH-induced intestinal carcinomas of 68 male Wistar rats were investigated by means of histochemical and electron microscopic properties to study their histogenesis and mucinogenesis. Among the epithelial glycoproteins, surface glycoprotein on the microvilli with glycocalyces was distinguishable from mucin in the cytoplasm based on histochemical staining and ultrastructural findings. From the phenotypic characteristics of glycoproteins, it was suggested that DMH-induced carcinomas could be classified into mucin producing carcinomas composed mainly of cells containing intracellular mucins and non-mucin producing ones. The mucin producing carcinomas consisted of poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous carcinoma presumably resulting from various degrees of differentiation into goblet cells. Their staining attitude varied and cells with neutral mucin, sialomucin and sulfated mucin were observed in the signet ring cell carcinoma. In addition, abnormal synthesis of glycoproteins was observed with ConA-paradox staining and PATS/PB/KOH/PAS. These histochemical properties suggested irregular synthesis of glycoproteins in carcinomas. In non-mucin producing carcinomas, glycoproteins were found mainly on the apical surface and contained sialomucin. A deviated differentiation into an absorptive cell could form an intracytoplasmic cyst filled with an aggregation of glycocalyces, so becoming another type of signet ring cell. (Author abstract) (28 Refs)

13. CARCINOGENICITY STUDY OF THE PESTICIDE MALEIC HYDRAZIDE IN MICE (MEETING ABSTRA

Cabral JR, Ponomarkov V, Tomatis L

International Agency of Research on Cancer, Lyon, France

Toxicologist; 2(1):62 1982

The carcinogenicity of the pesticide Maleic Hydrazide (was studied in C57BL/B6 mice. The free acid of MH was (98.5% pure; containing 0.6 ppm of hydrazine impurity). carcinogenicity experiments with MH included: a) subcut ous (sc) administration to 163 infant mice (5, 10, 20 and 20 MH per mouse on days 1, 7, 14 and 21 after birth, respect ly); and b) oral administration (gavage) to 82 male and fen mice, from weaning for life, at a weekly dose of 510 mg/kg MH. Groups of untreated and solvent controls were also av able. The experiments were terminated at 120 weeks. The administration to infant mice resulted in high preweaning m tality when compared with the respective controls. Liver-c tumors were observed in 7 males treated sc with MH. In t solvent-treated (tricaprylin) males, 3 liver-cell tumors were al found. One liver-cell tumor was seen in untreated male co trols. No liver-cell tumors were observed in treated or contr females. The difference in the incidence of liver tumors amon the various groups was not significant. When MH was admini tered orally (weekly for life), liver-cell tumor were observed i 4 males and in 2 females of the treated group, and in 1 mal and in 1 female of the solvent (olive oil) control group. In th respective untreated controls 1 male had a liver-cell tumor The incidence of tumor at sites other than the liver was simila in all groups. These results partially confirm the negative finding of a recent parallel study in rats. (1 Ref)

14. MORPHOLOGIC ANALOGY OF INTESTINAL TRACT CARCINOGENESIS IN ADENOMATOUS POLYPOSIS AND THE AZOXYMETHANE-TREATED RAT MODEL (MEETING ABSTRACT)

Hamilton SR, Stephens RB, Natuzzi E, Boitnott JK, Yardley JH

Department of Pathology, The Johns Hopkins University School of Medicine and Hospital, Baltimore, MD

71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

Parenteral administration to rodents of azoxymethane (AOM), a metabolite of dimethylhydrazine, provides a widely used model of colonic carcinogenesis. Unlike usual large bowel carcinoma in human beings (ULBC) but analogous to adenomatous polyposis (AP), the AOM model has a high incidence of multiple colonic carcinomas and proximal small bowel carcinomas, particularly with higher dosage of carcinogen. In this study, grossly normal colonic mucosa from 10 resections for ULBC, six prophylactic colectomies for AP, four AOM-treated, and four control rats was examined for dysplastic crypts in en face histologic sections oriented in the plane of the luminal surface. AOM-treated rats were male Fischer 344 rats given 10 weekly subcutaneous injections of 7 mg of AOM per kg, starting at 11 weeks of age and killed 24 weeks after the first dose. Grossly normal colonic mucosa showed 0.03 foci of dysplastic crypts per sq cm examined in ULBC, 3.0 in AP, 2.9 in AOM rats, and 0.05 in controls rats. Dysplastic crypts composed 0.005 per 1000 crypts examined from right colon in ULBC, 39 in AP, and 0.3 in AOM rats, intermediate to AP and ULBC. Grossly normal proximal small bowel mucosa in the AOM rats showed 1.1 dysplastic foci per sq cm. (no Refs)

15. DOSE RESPONSE STUDIES IN CARCINOGENESIS BY N-METHYL-N-FORMYLHYDRAZINE OF GYROMITRA ESCULENTA (MEETING ABSTRACT)

Toth B
University of Nebraska Medical Center, Omaha, NE
71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

The aim of these experiments was to ascertain whether the tumorigenic response of Swiss mice to N-methyl-N-formylhydrazine (MFH) is related to the dose levels. For this reason, MFH was administered in drinking water for life to mice from 6 weeks of age in the following doses: group 1, 0.0156; group 2, 0.0078; group 3, 0.0039; group 4, 0.002; group 5, 0.001; group 6, 0.0005; and group 7, 0.00025 per cent. Each group consisted of 100 mice (50 females and 50 males). The tumor incidences in the liver, lungs, gall bladder, bile ducts, and blood vessels were as follows. Group 1: 6, 13, 1, 1 and 1 per cent; group 2: 33, 50, 9, 7 and 4 per cent; group 3: 77, 46, 10, 7 and 21 per cent; group 4: 28, 76, 11, 4 and 27 per cent; group 5: 7, 75, 6, 3, and 23 per cent group 6: 0, 56, 0, 0, and 7 per cent; and group 7: 2, 58, 0, 0, and 4 per cent, respectively. Analysis of data indicates that up to a certain point an increase of the dose of the chemical is conversely related to tumor incidence and to the number of neoplastic tissues. Once a critical point is reached, however, the dose increase was accompanied by a significant decrease in the incidence and number of neoplastic tissues. One of the wild, edible false morel mushrooms G esculenta contains 0.05 per cent MFH. (no Refs)

HETEROCYCLIC COMPOUNDS

16. THE SIGNIFICANCE OF CHOLANGIOFIBROSIS AS A 'PRENEOPLASTIC LESION' (MEETING ABSTRACT)

Evans JG, Conning DM, Applebey EC
The British Industrial Biological Research Association, Woodmansterne Road, Carshalton, Surrey, SM5 4DS, England
Toxicologist; 2(1):100 1982

The histogenesis of carcinoma of liver having an adenomatous or ductal pattern is uncertain. Many consider that such tumors arise from bile ducts and is preceded by cholangiofibrosis; others consider that they are histological variants of hepatocellular carcinoma. The changes produced in the liver of rats by 3'Methyl-4-diaminoazobenzene (3'MeDAB) and by coumarin are compared. 3'MeDAB administration led to extensive oval cell proliferation and then to cholangiofibrosis. This was followed by hepatic nodules with variable enzyme patterns and later, trabecular and adenomatous or duct carcinoma. Coumarin induced cholangiofibrosis in which four distinct stages could be recognized. No altered foci, areas or nodules were seen, and no hepatocellular tumors developed. The ultrastructure appearance of cholangiofibrosis was compared with that of adenomatous areas of carcinoma. Cells forming the lining epithelium in both were similar. Carcinomas with ductal or adenomatous pattern were deep within unequivocal hepatocellular carcinoma and it is considered that they represent variants of such tumors. Occasionally ductal tumors appeared to arise within cholangiofibrosis. Possibly proliferating ducts exposed to a carcinogen may be susceptible to neoplastic change. It is concluded that most of tumors, induced by 3'MeDAB, even those are variants of hepatocellular carcinoma. (no Refs)

17. RAT CONCEPTUS DEVELOPMENT IN VITRO: COMPARATIVE EFFECTS OF ALKYLATING AGENTS.

Sanyal MK, Kitchin KT, Dixon RL
National Inst. Environmental Health Sciences, Research Triangle Park, NC
Rat Conceptus Development In Vitro: Comparative Effects of Alkylating Agents. Available from National Technical Information Service, Springfield, VA, as PB81-235780:, 8 pp., 1981.

Conceptuses removed from the rats in the 11th day of gestation were cultured in vitro for 2 days. Growth and differentiation of the major organs of the embryo in vitro resembled those developed in vivo. Embryonic development and organogenesis were markedly affected when the alkylating agents TEM (2,4,6-triethylenimino-1,3,5-triazine) and nitrogen mustard (mechlorethamine hydrochloride) were added to the culture medium. At concentrations of 1 and 5 micrograms/ml medium, these teratogens were highly embryotoxic and affected both growth and differentiation. DNA and protein content of embryos and yolk sacs was reduced significantly (p less than 0.001) from the controls Development of conceptuses in the culture medium that contained cyclophosphamide (0.35 mM) alone apparently were normal. However, addition of cyclophosphamide (0.35 mM), microsomes (0.5 mg protein/ml), and NADPH (1 mM) to the culture medium induced marked deleterious effects on the conceptus growth and differentiation. DNA and protein contents were significantly (p less than 0.001) reduced by the combined treatment indicative of formation of reactive metabolites and their interference with macromolecular biosynthesis. Aminopyrine which has not been shown to be teratogenic, in equimolar amounts to cyclophosphamide under identical conditions of culture, did not affect conceptus development. (Author abstract)

18. METABOLIC ASPECTS OF THE COMUTAGENIC ACTION OF NORHARMAN.

Sugimura T, Nagao M, Wakabayashi K
Natl. Cancer Center Res. Inst., Tsukiji, Chuo-Ku, Tokyo, Japan
Adv Exp Med Biol; 136(partB):1011-1025 1982

Microbial mutagenicity tests were conducted using norharman (beta-carboline) in the Ames Salmonella typhimurium assay with strain TA 98. Comutagenicity of norharman with aniline was demonstrated, and linear dose-response curves were obtained with the aniline metabolites phenylhydroxylamine and nitrosobenzene in the presence of 200 ug norharman. Norharman was comutagenic with o-toluidine, but not with m- or p-toluidines. It induced mutagenesis in yellow OB dye, but not red dye number 2, which does not yield either aniline or o-toluidine upon hydrolysis. 3-Aminopyridine and 2-amino-3-methyl-pyridine were mutagenic in the presence of norharman, but eight other aminopyridine derivatives were not. Diphenylnitrosamine (DPhN) and diphenylamine (DPhA) were mutagenic in the presence of norharman and S-9 mix, but not without both added components in the incubation medium. Mutagenicity of DPhN seems to be due to DPhA formed metabolically. Other strains of S typhimurium (TA 1538, TA 1978) showed sensitivity to aniline + norharman, and strains TA 100 and TA 1535 were totally unaffected. A mixture of microsomes + supernatant + NADPH yielded more revertants than microsomes alone, microsomes + NADPH, or supernatant + NADPH. (41 Refs)

19. COMPARISON OF THE MUTAGENIC POTENCY OF 2-CHLOROETHANOL, 2-BROMOETHANOL, 1,2-EPOXYBUTANE, EPICHLORHYDRIN AND GLYCIDALDEHYDE IN KLEBSIELLA PNEUMONIAE, DROSOPHILA MELANOGASTER AND L5178Y MOUSE LYMPHOMA CELLS.

Knaap AG, Voogd CE, Kramers PG
Natl. Inst. Public Health, P.O. Box 1, 3720 BA Bilthoven, The Netherlands
Mutat Res; 101(3):199-208 1982

The mutagenic activities of a series of chemically related mutagens in the Klebsiella pneumoniae fluctuation test, in the sex-linked recessive lethal test in Drosophila melanogaster, and in the HGPRT forward mutation test in L5178Y mouse lymphoma cells were tested. Compounds investigated included 2-chloroethanol (CE), 2-bromoethanol (BE), 1,2-expoxybutane (EB), epichlorohydrin (ECH), and glycidaldehyde (GA). In the fluctuation test, increased mutation rates were observed at concentrations of 5 and 0.1 milliM (mM) for CE and BE, respectively. Among the epoxides, the lowest effective concentrations were 1.0, 0.1 and 0.01 mM for EB, ECH and GA, respectively. In the sex-linked recessive lethal test, CE and BE were not mutagenic. EB at concentrations of 117 and 233 mM significantly increased mutation frequency. ECH had been shown by others to be mutagenic in this system, a result which was verified here. GA significantly increased mutation frequency at concentrations of 25 mM and higher. In the HGPRT mutation assay, induction of mutations were observed after treatment with EB and ECH, with ECH being the more mutagenic of the two compounds. (23 Refs)

20. STUDIES ON METABOLISM AND TOXICITY OF STYRENE. V. THE METABOLISM OF STYRENE, RACEMIC (R)-(+)-, AND (S)-(-)-PHENYLOXIRANES IN THE RAT.

Watabe T, Ozawa N, Yoshikawa K
Tokyo Coll. Pharmacy, Horinouchi, Hachioji-shi, Tokyo 192-03, Japan
J Pharmacobio Dyn; 5(2):129-133 1982

The stereochemical course of in vivo metabolism of styrene and optically active phenyloxiranes through the hydrolysis and conjugation routes was studied. (R)-(-)- and (S)-(+)-phenylethanediols and (R)-(+)- and (S)-(-)-phenyloxiranes with enantiomeric purities greater than 99% were synthesized and injected ip into rats at 2 millimole/kg, and urine specimens were examined for metabolites over a 24-hr period. The process was repeated for each compound in turn at weekly intervals. Evidence suggests that styrene, racemic phenyloxirane, and its (S)-isomer are metabolized via the hydrolysis route, and that the (R)-isomer is converted mainly to mercapturic acids via the conjugation route. Administration of styrene, racemic phenyloxirane, or its optically pure isomers leads to predominant formation of the mercapturic acid isomer MA-1, over the other regioisomer MA-2. A very large portion of injected styrene was metabolized via the mutagenic phenyloxirane to nontoxic compounds. (23 Refs)

21. MUTAGENICITY OF OXYGEN FREE RADICALS.

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Proc Natl Acad Sci USA; 79(9):2855-2859 1982

Paraquat (1,1'-dimethyl-4,4'-bipyridinium dichloride) was used as an intracellular generator of oxygen free radicals and was found to be highly mutagenic for Salmonella typhimurium. It caused both base-pair substitution and frameshift mutations. Paraquat was much more toxic and mutagenic in a simple nutritionally restricted medium than in a rich complex medium. The mutagenicity of paraquat was dependent upon the presence of a supply of both electrons and oxygen. Cells containing high levels of superoxide dismutase (superoxide:superoxide oxidoreductase EC 1.15.1.1) were more resistant to the toxicity and the mutagenicity of paraquat than were cells containing normal levels of this enzyme. The mutagenicity of paraquat thus appears to be due to its ability to exacerbate the intracellular production of superoxide radicals. (Author abstract) (41 Refs)

22. METABOLISM OF MUTAGENIC AMINO-GAMMA-CARBOLINES IN TRYPTOPHAN PYROLYSATES.

Kato R, Yamazoe Y, Ishii K, Mita S, Kamataki T, Sugimura T
Dept. Pharmacology, Sch. Medicine, Keio Univ., Tokyo 160, Japan
Adv Exp Med Biol; 136(partB):997-1009 1982

Metabolic activation of 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1) and 3-amino-l-methyl-5H-pyrido[4,3-b]indole (trp-P-2) by hepatic microsomes and reconstituted cytochrome P-450 systems and characterization of the mutagenic intermediate are described. The mutagenic metabolite of Trp-P-2 was shown to be a 3-hydroxyamine derivative. Studies of change in mutagenicity of Trp-P-1 and Trp-P-2 in the Salmonella typhimurium TA 98 assay after treatment of microsome donor rats with polychlorinated biphenyl, 3-methylcholanthrene, and phenobarbital suggested that the activated form of the indole compounds and the N-hydroxylation of Trp-P-2 were catalyzed by cytochrome P-448. Metabolic activation of Trp-P-1 and Trp-P-2 by NADPH-cytochrome P-450 reductase, cytochrome P-448, and NADPH was demonstrated. Genetic differences in formation of Trp-P-2 in mice, species differences in induction of benzo(a)pyrene hydroxylase and Trp-P-2 N-hydroxylase between rabbits and rats, and mutagenic activation by human liver microsomes were also shown. N-hydroxy-Trp-P-2, probably the free radical derivative, is probably an ultimate mutagen, but further metabolic activations by enzymes in the supernatant fraction and in S typhimurium TA 98 cannot be excluded. (20 Refs)

INORGANIC AGENTS AND PARTICULATES INCLUDING FIBERS

23. BIOLOGICAL EFFECTS OF TREMOLITE.

Wagner JC, Chamberlain M, Brown RC, Berry G, Pooley FD, Davies R, Griffiths DM
MRC Pneumoconiosis Unit, Llandough Hosp., Penarth, S. Glam. CF6 1XW, Wales
Br J Cancer; 45(3):352-360 1982

Tremolite is an amphibole which has been implicated in a variety of disease patterns in different parts of the world. It occurs in a number of phases, which are chemically identical but have specific physical characteristics. In an attempt to clarify the epidemiological findings, tremolite fibers of three specific forms - A, B and C- were characterized and studied for biological activity by: (i) in vivo intrapleural injection of rats (2 separate experiments -1 with poor survival). (ii) in vitro enzyme release from mouse peritoneal macrophages. (iii) in vitro giant-cell formation in A549 cultures, (iv) in vitro cytotoxicity for V79-4 cells. Sample C, which contained more long thin fibers than A and B, was alone in producing mesotheliomas. C, but not A or B, induced LDH and B-glucuronidase enzyme release, and induced giant cells. A was not cytotoxic, B moderately cytotoxic and C as highly cytotoxic as UICC crocidolite. The in vivo studies were marred by being split between two experiments, of which the second had poor survival. We are aware of the weakness of our in vivo data, but as Tremolite C was being considered for commercial use on the European market we felt it timely to submit our findings for publication. (Author abstract) (25 Refs)

24. EFFECTS OF COAL-COMBUSTION EFFLUENT ON PULMONARY CARCINOGEN METABOLISMS. QUARTERLY PROGRESS REPORT.

Colby HD
West Virginia Univ., Sch. Medicine, Morgantown, WV
Effects of Coal-Combustion Effluent on Pulmonary Carcinogen Metabolisms. Quarterly Progress Report. Available from National Technical Information Service, Springfield, VA, as DE81023278:, 3 pp., 1981.

This paper summarizes the direct effects of heavy metals in vitro on pulmonary, hepatic, and adrenal mixed function oxidases including those involved in the metabolism of various carcinogens such as benzo(a)pyrene. Apparent enzyme activity decreased as a function of increasing incubation time for the assay. These observations further illustrate the relevance of the preincubation type experiments described in previous reports. Thus, duration of exposure to metals appears to be an important determinant of the effects on microsomal carcinogen metabolism. Since many heavy metals have extremely long half-lives in tissues in vitro, prolonged duration of exposure may contribute significantly to the toxicity of heavy metals. (Author abstract)

25. A COMPARISON OF THE CYTOGENETIC RESPONSE TO ASBESTOS AND GLASS FIBER IN CHINESE HAMSTER AND HUMAN CELL LINES. DEMONSTRATION OF GROWTH INHIBITION IN PRIMARY HUMAN FIBROBLASTS.

Sincock AM, Delhanty JD, Casey G
Fund for Replacement of Animals in Medical Experiments, London SW20, England
Mutat Res; 101(3):257-268 1982

The response to asbestos and glass fiber was compared for Chinese hamster ovary cells (CHO), primary human fibroblasts (EN1, FPC1, 77LO, 59LO), and human lymphoblastoid cell lines (LIZ and 1526). Dusts employed were crocidolite and chrysotile. CHO cells exposed to the two asbestos fibers showed the expected high level of induced chromosome damage following 48 and 72 hr exposures. A lower level of damage was apparent in cells treated with glass code 100. Coarse glass fibers, code 110, produced no increased chromosome damage. Observed damage due to both types of asbestos and glass 100 consisted mostly of chromosome breaks and rearrangements, and polyploidy after asbestos but not glass. Presence of chrysotile or glass 100 at either 0.05 or 0.1 mg/ml in cultures of adult human fibroblasts resulted in very little increase in cell number over 4 days. Coarse glass code 110 had no effect on growth in fetal or adult human fibroblasts. Lowered cell numbers at harvest in cells treated with chrysotile asbestos of glass code 100 appeared to result from growth inhibition as evidence by lowered mitotic indices in such cultures. A possible reason for the refractoriness of human primary cell lines to cytogenetic damage induced by these agents may be the increased effectiveness of DNA repair in these lines compared to the permanent CHO lines. (19 Refs)

26. RETINYL PALMITATE AND ASCORBIC ACID INHIBIT PULMONARY NEOPLASMS IN MICE EXPOSED TO FIBERGLASS DUST.

Morrison DG, Daniel J, Lynd FT, Moyer MP, Esparza RJ, Moyer RC, Rogers W
Thorman Cancer Res. Lab., Trinity Univ., San Antonio, TX
Nutr Cancer; 3(2):81-85 1981

The influence of retinyl palmitate and ascorbic acid on the susceptibility of respiratory tract epithelium to the metaplastogenic, hyperplastogenic and tumorigenic effects of a 30-day exposure to fiberglass dust was tested in 60 male A-strain mice. Administration of retinyl palmitate or ascorbic acid, or both, significantly inhibited the development of metaplastic, hyperplastic and neoplastic lesions in these mice. (Author abstract) (21 Refs)

27. FURTHER STUDIES ON THE CO-TRANSFORMATION OF DISTANT MARKERS FOLLOWING THE EXPOSURE OF DNA TO CARCINOGENS INCLUDING CARCINOGENIC METALS (MEETING ABSTRACT)

Kubinski H, Kubinski ZO
University of Wisconsin Medical School, Madison, WI, 53706
Fed Proc; 41(3):685 1982

Exposure of Bacillus subtilis transforming DNA to chemical carcinogens produced a decrease in transforming activity of such DNA and a decrease in co-transformation of linked markers (tyr-trp). Under carefully controlled conditions an increase in co-transformation of distant (unlinked) markers (tyr-leu and trp-leu) was detected, indicating the formation of DNA-DNA complexes capable of penetrating into the interiors of the recipient cells. However, based on our studies of N-acetoxy-2-acetylaminofluorene - treated DNA, up to 80% of these complexes were eventually 'repaired', restoring the original chromosomal locations of these unlinked markers. Occasionally, the artificially linked pieces of DNA were inserted into adjacent loci in the recipients cell's chromosome. In separate studies, effects of various salts of chromium on the transforming DNA were investigated. An increased co-transformation of the unlinked markers was observed with Cr VI but not with Cr II or Cr III. The former, but not the latter are believed to produce tumors in humans. Thus, these observations support our earlier suggestion that only those mutational events which produce macromolecular complexes may be responsible for the malignant transformation in vivo. (no Refs)

28. MUTAGENICITY OF METAL SALTS IN THE L5178Y MOUSE LYMPHOMA ASSAY.

Oberly TJ, Piper CE, McDonald DS
Biochemical Toxicology, Dept. Toxicology, Eli Lilly and Co., PO Box 708, Greenfield, IN, 46140
J Toxicol Environ Health; 9(3):367-376 1982

The potential of 11 metals to induce forward mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells was studied. Strong positive responses at survivals greater than 10% were observed with CdSO4, K2CrO4, K2Cr2O7, and MnCl2. Weak positive responses, yielding 2-3x increases in the mutation frequency above the solvent control and at greater than 10% survival, were seen with HgCl2, NaAsO2, Na2HAsO4, and Pb(NO3)2. Negative responses were obtained with MgCl2, NaCl, and AlCl3. Because many of the suspect carcinogens studied here are present in the cities atmosphere, nonurban areas, and industrial plants, a strict evaluation of their genetic or carcinogenic risk to humans is necessary. The mouse lymphoma TK+/- system should be valuable in identifying and quantitating the mutagenicity of this class of environmental agents. (22 Refs)

29. EFFECTS OF PLATING EFFICIENCY AND LOWERED CONCENTRATION OF SALTS ON MUTAGENICITY ASSAYS WITH AMES' SALMONELLA STRAINS.

Witmer C, Cooper K, Kelly J
Dept. Pharmacology, Thomas Jefferson Univ., Philadelphia, PA, 19107
Adv Exp Med Biol; 136(partB):1271-1284 1982

Effects of altering the concentrations of total salts and histidine on number of spontaneous revertants, survival rates for the auxotrophic strains of bacteria, response to chromium(VI) (Cr VI) as a mutagen, and response to sodium azide (SA) as a mutagen in a standard Ames test (SAT) were studied. TA 100 which responds to both frame-shift and base-pair mutagens, and/or TA 1535 which detects base-pair mutagens only were used. For strains TA 100 and TA 1535 the actual numbers of spontaneous revertants that appeared after 48 hr of incubation varied as a function of the number of bacteria plated rather than appearing to be constant. The large numbers of isolated colonies appearing after 48 hr incubation when less than 10(4) bacteria were plated on the his+ minimal agar with conditions identical to those described for TA 100 and TA 1535 are shown. Most strains tested survived poorly with lowered salts available and apparent survival was dependent on both the histidine and salts concentrations. The apparent low survival rates of all strains tested except for TA 1535 on the 1/3 (S) plates after 48 hr of incubation with 0.045 milliMoles histidine are presented. The surviving colonies when the plates were reincubated and recounted at 72 hr are shown as well as the apparent percentage survival of five strains in a typical series of experiments. An example of the use of lowered concentrations of salts in detecting mutagenicity of Cr VI compounds is presented. Results with SA indicated that decreased concentration of salts resulted in decreased response to SA as a mutagen. Results indicated that some inorganic compounds can be more accurately detected as mutagens using modified conditions of SAT. (11 Refs)

30. BIOCHEMICAL AND HISTOPATHOLOGICAL RESPONSE TO CHRYSOTILE INGESTION IN GUINEA PIGS.

Saxena KC, Srivastava L, Dogra RK
Industrial Toxicology Res. Centre, Mahatma Gandhi Marg, Post Office Box 80, Lucknow 226001, India
Ind Health; 20(1):19-25 1982

The biochemical and histopathological changes induced by ingested asbestos (chrysotile dust, 500 mg) were studied in guinea pigs over a period of 24 hr. A significant increase in the volume of gastric juice, free and total acidity, and peptic activity associated with a decrease in the mucin content of gastric juice, after chrysotile ingestion, indicates that these changes may be related to the dissolution and/or disposal of chrysotile dust in the stomach. Most changes occurred at 12 hr, the period of maximal dissolution of chrysotile dust as evidenced by the leaching of nickel. A rise in ATPase activity of the gastric mucosa also occurred at 12 and 24 hr. Damage to the mucosal cells was evident histopathologically 12 hr after chrysolite ingestion, and was probably due to the injury (erosion or penetration) caused by the asbestos fiber in the gastric mucosa. Restoration and reversal of changes in volume, free acidity, gastric juice mucin content, and gastric mucosal injury occurred at 24 hr. Apparently this occurred because most of the chrysotile had been expelled from the stomach. The role of gastric juice acidity and nickel dissolution in the production of gastric ulceration and carcinoma from ingested chrysotile were discussed. (22 Refs)

31. REVIEW OF NICKEL TOXICOLOGY (MEETING ABSTRACT)

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J Occup Med; 24(4):331 1982

Nickel carbonyl poisoning and nickel dermatitis have long been known. The main emphasis of this paper will be on the recent interest in nickel carcinogenesis. NIOSH has estimated that 250,000 workers in the United States are exposed to inorganic nickel. Numerous animal studies have clearly identified the carcinogenic activity of nickel. More recently, epidemiological and in vitro studies indicate that the so-called insoluble nickel compounds are much more active biologically. Nickel analysis in biological tissue has been refined so that small differences in the environment are demonstrated in blood and urine. Aside from nickel carbonyl poisoning, there is no dose response relationship between biological levels of nickel and specific clinical manifestations of disease. Confounding the tissue is the relationship between total body burden of nickel and serum levels, and further, no firm correlation exists at the moment between environmental monitoring and biological monitoring of insoluble nickel compounds. (no Refs)

AMIDES, CARBAMATES AND UREAS

32. EFFECT OF TISSUE-SPECIFIC LUNG FACTOR CONTACTIN ON MORPHOGENESIS AND SENSITIVITY OF MOUSE EMBRYO LUNGS TO TOXIC AND CARCINOGENIC EFFECT OF URETHANE IN ORGAN CULTURES.

Kolesnichenko TS, Iamskova VP, Chesheva NK

All-Union Cancer Res. Center, Moscow, USSR

Eksp Onkol; 4(2):23-27 1982

The effect of highly purified tissue-specific factor isolated from the lungs of random-bred rats (contactin) was studied in the organ cultures of lung tissue of mice A embryo. Culturing of lung explants in the medium containing urethane resulted in a marked decrease of survival of test cultures. Contactin produced almost a 4x decrease of urethane toxicity. Culturing of lung tissue from mice embryo subjected to a transplacental exposure to urethane showed development of diffuse hyperplasias and microadenomas. Contactin decreased the incidence of dystrophic changes and increased the incidence of hyperplastic changes. Contactin did not enhance the incidence of microadenomas. The enhancement of carcinogenic effect of urethane was probably associated with the growth-stimulating activity of contactin. Low concentration of contactin (10(-8) mg protein/mg) induced hyperplasia only in the bronchial epithelium, while higher concentration of contactin (10(-5) mg protein/mg) induced hyperplastic changes both in the bronchial and in the alveolar epithelium. (16 Refs) (In RUS)

33. EFFECT OF 4'-HALOGEN SUBSTITUTION ON THE MUTAGENICITY OF TRANS-4-ACETAMIDOSTILBENE AND TRANS-4-(N-HYDROXYACETAMIDO)STILBENE IN THE SALMONELLA TYPHIMURIUM TEST SYSTEM.

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J Med Chem; 25(5):593-595 1982

The effect of halogen substituents placed at the 4' position of trans-4-acetamidostilbene (1, AAS) to alter the pattern of biotransformation and thus the mutagenicity of these derivatives was evaluated by comparing the mutagenic effects of 1 on Salmonella typhimurium TA-100 with the corresponding 4'-F (2), 4'-Cl (3), and 4'-Br (4) analogues. The mutagenic properties of trans-4-(N-hydroxyacetamido)stilbene (5) and its 4'-F (6), 4'-Cl (7), and 4'-Br (8) derivatives were also evaluated in this system. Both the amides (1-4) and hydroxamic acids (5-8) required the presence of a metabolic activating system prepared from hamster liver in order to produce a mutagenic effect. All of these compounds were mutagenic to TA-100. Their mutagenic potencies were markedly influenced by the 4'-halogen substituents, the relative mutagenic potencies of the amides being 2 (4'-F) greater than 1 (4'-H), 3 (4'-Cl) greater than 4 (4'-Br), while the hydroxamic acids followed the order of 1 (4'-H) greater than 2 (4'-F) greater than 3 (4'-Cl), 4 (4'-Br). (Author abstract) (17 Refs)

34. IMMUNOSUPPRESSIVE PROPERTIES OF POLAR ORGANIC COMPOUNDS THAT INDUCE CELLULAR DIFFERENTIATION IN FRIEND ERYTHROLEUKEMIA CELLS.

Suthanthiran M, Rubin AL, Novogrodsky A, Stenzel KH
Rogosin Kidney Center, Dept. Medicine and Biochemistry, Cornell Univ. Medical Coll., New York, NY, 10021
Transplantation; 33(5):534-540 1982

We studied the effect of several polar organic compounds, known to induce erythroid differentiation in Friend leukemia (FL) cells, on in vitro human lymphocyte responses and on skin graft survival in mice. The short chain fatty acids, butyric acid (BA), propionic acid (PA), valeric acid, and the polar organic solvents, dimethyl sulfoxide, dimethylformamide, and dimethylacetamide, all mediated significant inhibition of alloantigen-induced proliferation and generation of cytotoxic T lymphocytes (CTLs) in human primary and secondary mixed lymphocyte culture (MLC) reactions. Hexamethylenebisacetemide, another potent inducer of differentiation in FL cells, also mediated significant suppression. Inhibition of MLC with polar organic compounds was accomplished at concentrations known to induce differentiation in FL cells and that are not cytotoxic to peripheral blood mononuclear cells. In distinct contrast, agents that are structurally related to BA, but that do not induce differentiation in FL cells, such as caproic acid, beta-OHBA, gamma-amino BA, and isobutyric acid, did not exhibit immunosuppressive properties. Pokeweed mitogen-driven polyclonal B cell activation was also suppressed by agents that induce erythroid differentiation in FL cells. In addition to potent in vitro immunosuppressive properties, supplementation of drinking water with BA or PA resulted in prolongation of full-thickness skin grafts in DBA/2 (H-2d) to C57BL/6 (H-2b) donor-recipient combinations. Our findings indicate that polar organic compounds that induce differentiation in FL cells are potent immunosuppressive agents. (Author abstract) (21 Refs)

35. SUBCHRONIC TOXICITY OF ETHYLENETHIOUREA IN MICE AND RATS (MEETING ABSTRACT)

Kurtz P, Peters A, Donofrio D, Chhabra R
Battelle Columbus Laboratories, Columbus, OH, 43201
Toxicologist; 2(1):96 1982

Ethylenethiourea (ETU) is a decomposition product of ethylenebisdithiocarbamate agricultural fungicides and has been previously reported to produce thyroid carcinoma in the rat. This study examined possible differences between rat and mouse in susceptibility to the effects of subchronic exposure to ETU in dosed feed. In a preliminary study groups of 10 rats and 10 mice were continuously exposed to ETU concentrations between 500 and 8000 ppm for 14 days. Exposure to the three highest concentrations produced total (8000 and 4000 ppm) or partial (2000 ppm) group mortality in rats but no mortality in mice. The greater toxicity of ETU in rats is consistent with reports that this compound has a longer half-life in rats than in mice. In the 13 week subchronic study, 10 rats per sex were exposed to ETU concentrations ranging from 60 to 750 ppm and ten mice per sex were exposed to doses ranging from 125 to 2000 ppm. Growth depression was evident in both male and female rats exposed to 750 ppm and in male rats exposed to 500 ppm. Weight gain was mildly depressed in mice exposed to 2000 ppm. Thyroid follicular hyperplasia was seen in all the rats of the 750 and 500 ppm groups and in 16/20 rats of the 250 ppm group. Thyroid adenomas occurred in 65%, 45% and 35% of the rats in these groups, respectively. In mice, thyroid follicular hyperplasia was seen in all of the 2000 ppm group in 19/20 mice from the 1000 ppm group. (no Refs)

36. ACRYLAMIDE AS A TUMOR INITIATOR IN THE MOUSE SKIN (MEETING ABSTRACT)

Bull RJ, Robinson M, Cmehil D
Health Effects Research Laboratory, Cincinnati, OH, 45268
Toxicologist; 2(1):103 1982

Acrylamide is a common monomeric unit of a variety of commercial products. It has been recognized for sometime as a neurotoxin. However, its structural resemblance to ethyl carbamate (urethane), an established tumor initiator, led us to examine the carcinogenic properties of this chemical in the mouse skin. A small scale experiment was carried out to test the hypothesis that acrylamide may act as a tumor initiator. The study involved administration of a single dose of 30 mg/kg by each of 3 routes of exposure (oral, intraperitoneal and topical) to female SENCAR mice. These initiating doses were followed in 2 weeks by repeated application of 1 ug 12-O-tetradecanoyl phorbol-13-acetate (TPA) 3 times weekly for 20 weeks. At 32 weeks following the start of promotion the following cumulative tumor counts (papillomas) were noted: Oral gavage, acrylamide 8 animals in 40 (8/40) with tumors and average of 0.25 tumors per animal; distilled deionized H2O (DH2O) 6/20 and 0.35; IP, acrylamide 18/40 and 0.55, DH2O 3/20 and 0.20; topical acrylamide 6/40 and 0.15 and acetone 3/20 and 0.25. It appears from this data that acrylamide via the IP route is capable of initiating tumors. As in previous studies with urethane, the potency of acrylamide is greater by a systemic route than the topical route of exposure. (no Refs)

AMINO ACID ANALOGS AND MODIFIED NUCLEIC ACID CONSTITUENTS

37. TRANSFORMATION BY ETHIONINE AND S-ADENOSYLETHIONINE OF RAT LIVER EPITHELIAL CELLS IN CULTURE (MEETING ABSTRACT)

Wilson MJ, Brown JD, Poirier LA
National Cancer Institute, Frederick Cancer Research Facility, Frederick, MD, 21701
Fed Proc; 41(3):281 1982

A normal line of rat liver epithelial cells was grown in Williams' Medium D in the presence and absence of the hepatocarcinogen DL-ethionine. The treated cells were exposed for 12 weeks to 2 levels of ethionine, 5.0 and 7.5 mM. The cultures were then maintained in carcinogen-free medium for an additional 31 weeks. At 4 week intervals throughout the experiment the cells were tested for transformation by: 1) carcinoma production following subcutaneous injection of cells into syngeneic hosts and 2) growth in soft agar. Twenty-one weeks after cessation of treatment, growth in soft agar was observed in cultures treated with both levels of ethionine, and tumors were produced in animals injected of ethionine, and tumors were produced in animals injected with cells treated with 7.5 mM ethionine. Control cultures remained untransformed throughout the experiment. The experiment was repeated using medium in which methionine was replaced by homocysteine. Ethionine was more toxic under these growth conditions; therefore, levels of 0.2 and 0.375 mM L-ethionine were used. In the same study cells were also treated with 0.065 and 0.2 mM L-S-adenosylethionine. Both compounds resulted in transformation of the hepatocytes 8 weeks after cessation of treatment. The results indicate that ethionine transforms hepatocytes in culture and that S-adenosylethionine may be a proximal carcinogenic metabolite of ethionine. (no Refs)

38. DIFFERENCES IN INTRACELLULAR RETENTION OF L-AZASERINE CORRELATE WITH GAMMA-GLUTAMYL TRANSPEPTIDASE ACTIVITY (MEETING ABSTRACT)

Perantoni A, Rice JM, Curphey TJ
National Cancer Institute, Frederick, MD 21701
Fed Proc; 41(3):336 1982

L-Azaserine toxicity and carcinogenicity correlate positively with cellular levels of gamma-glutamyl transpeptidase (GGT). Interest in the basis for this relationship has led to an investigation of the postulated role of GGT in transport of neutral amino acids. Cell lines with difference GGT activities and GGT-deficient cell strains derived by azaserine treatment of TuWi, a human nephroblastoma line high in GGT, were used to test a possible role of GGT in azaserine transport. Uptake of azaserine, a substrate for GGT, does not correlate with cellular GGT activity. Loss of azaserine from cells following its removal from culture medium, however, is correlated with enzyme activity. After exposure to azaserine (0.6 mM, 3 hr) and within 30 min of its removal from medium the hamster lung fibroblast V79, rat liver-derived ARL6T, and TuWi (GGT activities of 0.5, 10, and 46 nmol product/min/mg protein, respectively) retained 3.5, 5.7, and 7.1 nmol azaserine/mg protein. Cell strains of TuWi with GGT activities of 12, 25, 26, and 27 retained azaserine levels of 4.8, 5.5, 6.0 and 6.2 nmol/mg protein, respectively. The same qualitative pattern is maintained as cells continue to lose azaserine with time. Analysis of culture supernatants suggests that the azaserine remains intact. These results are consistent with a role for GGT in the intracellular retention of azaserine and perhaps other neutral amino acids. (no Refs)

39. ETHIONINE INHIBITS IN VIVO METHYLATION OF NUCLEAR PROTEINS.

Tuck MT, Cox R

Cancer Res. Lab., Veterans Admin. Medical Center, Memphis, TN, 38104

Carcinogenesis; 3(4):431-434 1982

Nuclear protein methylation was studied in regenerating rat liver by giving [methyl-3H]methionine 45 hr after partial hepatectomy. Ethionine, a liver carcinogen, has been shown to alter the methylation patterns in a basic protein (histone) fraction, as well as an acidic protein (non-histone) fraction present in a 0.25 N HCl nuclear extraction. The proteins present in the 0.25 N HCl extraction were separated by chromatography using Bio-Rex 70 cation exchange column. Polyacrylamide gel electrophoresis and total amino acid analysis showed the first protein fraction contained acidic large mol wt non-histone proteins, while the second fraction contained basic small mol wt histone proteins. Both fractions were then hydrolyzed, and the amino acids chromatographed on an Aminex A-5 cation exchange column. The histones were found to contain epsilon-N-mono, di and trimethyllysine derivatives; whereas the non-histone fraction contained these lysine derivatives and an additional basic amino acid identified as NG,NG-dimethylarginine. Ethionine (0.5 mg/g body wt) was found to inhibit in vivo methylation of lysine to form epsilon-N-mono, di and trimethyllysine, 46, 52 and 68%, respectively. The formation of NG,NG-dimethylarginine was inhibited by 85%. Ethylation of these proteins was also studied by giving [ethyl-3H]ethionine. After hydrolysis, the non-histones were found to contain a labeled lysine and arginine derivative, but in the histone fraction only labeled lysine was found. (Author abstract) (21 Refs)

40. TERATOGENIC EFFECTS OF AZASERINE IN THE SYRIAN GOLDEN HAMSTER (MEETING ABSTRACT)

Roebuck BD, Carpenter SJ

Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, NH

Toxicologist; 2(1):117 1982

Azaserine is a potent pancreatic carcinogen in the rat. The Syrian golden hamster, however, has been shown to be resistant to the carcinogenic effects of this drug. The present study was undertaken to determine if the hamster is also refractory to the teratogenic properties of azaserine. Pregnant hamsters were injected iv or ip with single doses of azaserine (1.5-3.0 mg/kg) on either day 7, 8 or 9 of gestation. The hamsters were sacrificed on day 12 of the 16 day gestation period and a count made in each hamster of viable and resorbing (dead) fetuses. Live fetuses were examined for growth retardation and gross external malformations. Azaserine was found to have both embryo-lethal and teratogenic effects in the hamster. Fetal mortality in azaserine treated dams ranged from 17 to 100% varying with the dosage, route of administration and day of gestation. For fetal mortality, a dose-response relationship was shown. Fetal mortality among the controls did not exceed 5%. The incidence of fetal abnormalities ranged from 9 to 100% in treated hamsters, versus 3% in controls. The most common fetal abnormalities were runting and limb defects. These results, compared with previous studies on rats, suggest that azaserine is equally embryolethal in the hamster and the rat. The hamster is also more resistant to the teratogenic actions of azaserine than the rat. (no Refs)

41. L-AZASERINE INDUCTION OF LAMBDA PROPHAGE: ENHANCING ACTIVITY OF TISSUE EXTRACTS FROM NORMAL AND DIETARY METHYL GROUP DEFICIENT RATS (MEETING ABSTRACT)

Salt JL, Rogers AE, Cruz B, Roebuck BD
Department of Biology and Nutrition, M.I.T., Cambridge, MA
Toxicologist; 2(1):123 1982

L-azaserine is a potent carcinogen that, in bacteria, can cause mutation and bacteriophage induction without prior activation by mammalian enzymes. However, we found that rat tissue extracts markedly enhanced azaserine phage inducing activity. In the Inductest of Moreau, et al, prophage induction in Escherichia coli (lambda) by azaserine alone began only after a 40-60 minute lag. Addition of rat hepatic post mitochondrial supernatant (S9) enhanced induction by reducing the lag; more than 50% of the population was induced by 40 minutes. Preparations from rats fed a diet deficient in methyl groups were about twice as effective in the enhancement of induction at a given time as S9 fractions from control animals. Enhancing activity was found also in pancreatic extracts, but in lesser amount than in liver and was unaffected by diet. Most of the S9 activity was found to be in the cytosol; it was destroyed by trypsin. Hepatic cytosol enhanced also azaserine mutagenesis in Salmonella typhimurium, at short times of exposure. Under Inductest conditions cytosol promoted incorporation of label from 14C-azaserine into the bacteria, most of it into acid insoluble material, usually after a 15-20 minute lag. This pattern differed from the rapid active transport and incorporation of the amino acids tryptophan and proline into bacteria that was not affected by cytosol. (no Refs)

ALIPHATIC HALOGEN COMPOUNDS

42. CARCINOGENICITY OF FLUOROCARBONS: ASSESSMENT BY SHORT-TERM IN VITRO TESTS AND CHRONIC EXPOSURE IN RATS (MEETING ABSTRACT)

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Toxicologist; 2(1):106 1982

Twenty-one fluorocarbons were evaluated for mutagenic activity using Salmonella typhimurium. Twelve of these were also assessed in the BHK21 cell transformation assay. Monochlorodifluoromethane (FC-22), chlorofluoromethane (FC-31), 1-chloro-1,1-difluoroethane (FC-142b), 1,1-difluoro-2-chloroethane (FC-142) and 1,1,1-trifluoroethane (FC-143a), showed mutagenic activity towards Salmonella and FC-31 and FC-142b were positive in the BHK21 test. The in vivo carcinogenicity of some of these chemicals was also assessed by a long-term bioassay. Wistar rats (40/sex/group) were dosed by gavage with 300 mg/kg bodyweight of 3% w/v in corn oil FC-22, FC-31, FC-133a (2-chloro-1,1,1-trifluoroethane), FC-134a (1,1,1,2-tetrafluoroethane) and FC-143a, five days a week for one year. One undosed and two dosed control groups were employed. The study was terminated at 126 wks. Rats dosed with FC-31 showed a high incidence of stomach squamous cell carcinomas and fibrosarcomas. Female rats dosed with FC-133a had a markedly increased incidence of uterine adenocarcinomas while the males of the group had a greatly increased incidence of testicular interstitial cell tumors and all had marked testicular atrophy. Carcinogenicity was not seen with any of the other fluorocarbons. (no Refs)

43. COVALENT BINDING OF CCL4-INTERMEDIATES TO REDUCED PYRIDINE NUCLEOTIDES IN MOUSE LIVER.

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Adv Exp Med Biol; 136(partA):769-777 1982

The effects of CCl4-intermediates on RNA in a microsomal system in vitro and effects of CCl4 on rat liver DNA in vivo were investigated. Incubation of CCl4 with mouse liver microsomes resulted in pronounced covalent binding to proteins and lipids. Only very small amounts of labeled metabolites were found to be associated with phenol-extracted endogenous ribosomal RNA and exogenous transfer RNA which was added to the microsomal incubation mixture. Separation of the individual components on a cellulose column showed that binding had occurred not to hydrolyzed ribonucleotides but exclusively to reduced nucleotides. Results and the observation that no radioactivity was associated with the hydrolyzed adenine moiety of pyridine nucleotides indicated that CCl4-metabolites bind exclusively to nicotinamide ring. The distribution of the electron density in the ring suggested that the metabolites are bound either as radicals to the 5-position or as carbenes to the 5,6-double bond. No covalent binding of CCl4-metabolites to oxidized pyridine nucleotides was observed. Covalent binding to reduced pyridine nucleotides required NADPH and was accelerated by the addition of NADH. A modification of the alkaline filter elution test was used to study damage to liver DNA of rats treated with 4 mg CCl4/kg body wt. Results showed that CCl4 treatment does not induce strand breaks in liver DNA. No cross-links in liver DNA which might have occurred as a result of malondialdehyde formation following CCl4-induced lipid peroxidation could be detected. As CCl4-metabolite-pyridine nucleotide adducts appear to inhibit the action of pyridine nucleotide-dependent enzymes, exposure of animals to CCl4 might inhibit these enzyme systems. (17 Refs)

44. THE ACTIVATING ROLE OF GLUTATHIONE IN THE MUTAGENICITY OF 1,2-DIBROMOETHANE.

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Adv Exp Med Biol; 136(partA):809-820 1982

Role of conjugation to glutathione (GSH) in the mutagenicity of 1,2-dibromoethane (DBE) was investigated and some preliminary results on the occurrence of reactive GSH conjugates in vivo are reported. The activity of GSH-S-transferase in vitro, synthesis and reactions of model conjugates, mutagenicity of DBE, and DNA binding of DBE are reviewed. DBE was tested to determine which mechanism is responsible for the activation. Results indicated that the enhancement of mutagenic activity is caused by conjugation to GSH. The spontaneous binding of DBE to DNA may result from initial reactions with sulfur or nitrogen nucleophiles, giving rise to the same type of half-mustards as the GSH conjugates. Rats excreted 30-50% of DBE in the form of mercapturic acid. Direct conjugation of GSH with DBE and DBE oxidation followed by loss of hydrogen bromide may lead to the structure of the metabolite. Excretion of N-acetyl-S-2-hydroxyethyl-L-cysteine by male Wistar rats after administration of 0.1 millimole DBE/rat with and without pretreatment with 10 g 1-phenylimidazole/rat is presented. Results show that direct conjugation of DBE to GSH and thus formation of the reactive 2-halogenothioether in vivo is a viable pathway of metabolization. Conjugation to GSH can give rise to the formation of reactive glutathione conjugates, provided a second leaving group is present at the carbon atom next to the one where sulfur substituent becomes attached. (21 Refs)

45. EFFECTS OF CHLORINATED PARAFFINS ON SOME DRUG-METABOLIZING ENZYMES IN RAT LIVER AND IN THE AMES TEST.

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Adv Exp Med Biol; 136(partA):821-828 1982

Influence of chlorinated paraffins (CP) on induction of drug-metabolizing enzymes in rat liver and mutagenic effect in the Ames test are discussed. Results of induction of drug-metabolizing enzymes in rat liver by CP are presented. The liver-somatic index increased and the amount of cytochrome P-450 was not changed. The activity of microsomal epoxide hydrolase was not affected by treatment with Cereclor 42, but the activity increased 30, 90, and 200-330% after treatment with Cereclor S58, 70, and 70L, respectively. SDS-polyacrylamide gel electrophoresis was performed to compare the proteins of liver microsomes from control and induced rats. The same polypeptide pattern was observed in both groups of animals and some of the bands were increased in the treated rats. No toxic effects were noted in any of the strains in the Ames test and no differences in the number of revertants with the strains TA 1537 and TA 100 were observed. Strain TA 98 showed a slight increase in the number of revertants in the presence of S-9 fraction. This low increase may have arisen by chance since no dose related effects were observed with Cereclor 70L. Furthermore the lack of toxic effects may indicate that paraffin does not penetrate into bacterial cells. Possible modes of metabolism of Cereclor 70L include dechlorination and oxidation of the carbon chain. Metabolism of CP may also be related to their ability to induce epoxide hydrolase and glutathione S-transferase. (16 Refs)

46. METABOLIC ACTIVATION AND DEACTIVATION MECHANISMS OF DI-, TRI-, AND TETRACHLOROETHYLENES.

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Adv Exp Med Biol; 136(partA):659-666 1982

Research on the metabolic transformation of mutagenic and carcinogenic chlorinated ethylenes has produced a general scheme in which epoxides, formed from chlorinated ethylenes by monooxygenases, can undergo subsequent transformation via three routes: (1) alkylating substitution with nucleophilic sites of macromolecules; (2) rearrangement, by intramolecular chlorine migration, to chlorinated aldehydes or acyl chlorides; (3) conjugation with glutathione or cysteine and subsequent metabolic transformation, to mercapturic acid derivatives. It is hypothesized that differences in mutagenic activity or inactivity of chlorinated ethylenes may be explained by differences in reactivity of the epoxides. Recent work on the metabolic activation of 1,1-dichloroethylene, trichloroethylene, and tetrachloroethylene is summarized. These in vitro and in vivo experiments have led to the discovery of a variety of new metabolites and a partial revision of the former concepts of metabolic transformation mechanisms. (17 Refs)

47. METABOLISM OF VINYL HALIDES: IN VITRO STUDIES ON ROLES OF POTENTIAL ACTIVATED METABOLITES.

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Adv Exp Med Biol; 136(partA):685-692 1982

Mixed-function oxidation of toxic and carcinogenic vinyl halides is thought to be responsible for the mutagenesis and irreversible binding of metabolites observed with these compounds. One suggested reactive metabolite is a 2-haloethylene oxide, which in turn may rearrange to a 2-haloacetaldehyde, both compounds reacting with nucleophilic targets. Studies are reported examining the ability of purified enzymes to specifically destroy the postulated reactive intermediates of vinyl chloride and vinyl bromide in rat liver microsomal systems, utilizing irreversible binding of vinyl halide labels to protein and DNA as indices of activation. The results are consistent with the view that, in the liver microsomal system, the 2-haloethylene oxides are the species predominantly involved in DNA binding. 2-Haloacetaldehydes, formed from the 2-haloethylene oxides by halogen migration rearrangement, are the primary metabolites binding to protein and glutathione. The 2-haloacetaldehydes, being the more stable intermediates, probably play a significant role in binding to sites outside of the hepatocyte. (22 Refs)

48. THRESHOLD LEVELS IN TOXICOLOGY: SIGNIFICANCE OF INACTIVATION MECHANISMS.

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Adv Exp Med Biol; 136(partB):1389-1398 1982

Various in vitro test systems demonstrated that metabolic inactivation of chemicals may prevent toxic effects of reactive intermediates when present in low levels, while inactivation may be overcome at high levels. Reactive oxygen species formed during monooxygenase-mediated metabolism of chemicals can induce DNA repair activity in the human lymphoblastoid cell line NC37 BaEV. Addition of catalase, glutathione, and superoxide dismutase prevents hydroxyurea-induced DNA repair, indicating that H2O2 or reactive oxygen species deriving from H2O2 are likely to be genotoxic agents. Toxicity studies of chloroprene indicated that no carcinogenic effect could be found, while a slight mutagenic effect was noted with Salmonella typhimurium strains without metabolic activation. This finding is likely due to inactivation by glutathione-conjugations. In the presence of glutathione, chlorodinitrobenzene was not mutagenic in Salmonella typhimurium. However, at concentrations exceeding those of glutathione, it was increasingly mutagenic. Irreversible binding of naphthalene was increased by suppression of glucuronidation and sulfation in isolated hepatocytes. These findings demonstrate that two threshold doses can be observed: a no-effect level and a level at which the toxic effects disproportionally increase when high concentrations of a chemical are present and inactivation can be overcome. The relevance of extremely high doses often used in animal experiments for studying embryo toxicity or in other chronic toxicity studies is questioned. (25 Refs)

49. TRANSLATION OF PHARMACOKINETIC/ BIOCHEMICAL DATA INTO RISK ASSESSMENT.

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Adv Exp Med Biol; 136(partB):1399-142[illegible]982

Basic pharmacokinetic principles and biochemical mechanisms which must be considered in order to adequately evaluate the risk of exposure to man from potentially carcinogenic chemicals are reviewed. Dose-independent and dose-dependent pharmacokinetics are discussed. A theoretical model describing the pharmacokinetics of chemical interactions with macromolecules is presented, with emphasis on the importance of knowledge of the dose-related fate of a chemical and its macromolecular target site. Two basic mechanisms responsible for the observation of increased tumor frequencies in the typical animal bioassay are the genetic or genotoxic mechanism and the mechanism through which tumors are produced by a cytotoxic or nongenetic effect. Studies of vinyl chloride (VC) and chloroform illustrate the use of pharmacokinetic and biochemical data of the mechanisms of tumorigenesis to understand the differential carcinogenic response between species with emphasis on risk assessment. With VC, the incidence of hepatic angiosarcomas in humans can be predicted with reasonable accuracy using a probit percentage incidence model. The primary mechanism by which chloroform produces tumors in animal bioassays appears to be recurrent cytotoxicity accompanied by chronic tissue regeneration. The original risk estimation of chloroform was found to be unjustified and overestimated when the species dependent metabolic activation of the compound and the biochemical nature of chloroform-induced tumorigenicity were considered. (38 Refs)

POLYHALOGENATED RING COMPOUNDS INCLUDING INSECTICIDES

50. MONOOXYGENASE AND EPOXIDE HYDROLASE REGULATION IN PRIMARY FETAL RAT LIVER CELL CULTURE.

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Adv Exp Med Biol; 136(partA):87-98 1982

Presence of cytochrome P450 (CP450) was studied in fetal hepatocyte culture and measurements of aryl hydrocarbon hydrolase (AHH), ethoxycoumarin deethylase, aldrin epoxydase, and epoxide hydrolase (EH) activities were measured. The level of CP450 content in primary fetal liver cell culture was stable and did not significantly differ from that found in fetal liver used for the culture preparation. High concentration of phenobarbital (PB) induced both AHH and EH activities, whereas benz(a)anthracene acted preferentially , and 2,3,7,8-tetrachlordibenzo-p-dioxin selectively on AHH activity. AHH and EH activities were modified by addition of dexamethasone. The enzyme activities were first inhibited and then induced when the corticoid concentration was raised from 10(-10) to 10(-4) M. The same shift in the AHH inhibition in vitro by alpha-naphtoflavone (ANF) and metyrapone (MTR) was observed, whether the dexamethasone treatment was carried out in the presence or in the absence of serum. The action of other hormonal steroids on both AHH and EH activities was also studied. The same effect was observed with hydrocortisone; a shift in sensitivity of the control and PB-induced AHH activity in vitro from ANF to MTR, and a fall in the control and PB-induced EH activity. Sex hormones, testosterone (TS) and estradiol (ED) slightly induced the AHH activity and decreased the extent of AHH and EH induction by PB. TS and ED did not decrease the EH activity and did not shift in vitro the sensitivity of either the control or the PB-induced AHH to the inhibitors. According to these observations, glucocorticoids are some of the physiological stimuli controlling the expression of drug metabolizing enzyme activities in the perinatal period of life. (21 Refs)

51. CARBARYL BINDS TO PROTEINS OF HUMAN CELLS IN CULTURE BUT CHLORINATED ORGANIC CHEMICALS DO NOT.

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Bull Environ Contam Toxicol; 28(4):500-503 1982

Radiolabeled carbaryl became highly bound to protein isolated from cultured human embryonic lung diploid cells (HEL 299), whereas benzo(a)pyrene showed less binding. No binding of the following chlorinated chemicals was detected: 2,4-dichlorophenoxy-2-14C-acetic acid, dichlorodi-U-14C-phenyltrichloroethane, hexachlorobenzene-14C(U), or polychlorinated biphenyl-14C(U). (10 Refs)

52. ESTRADIOL EFFECTS OF 2,3,7,8,TETRACHLORODIBENZO-P-DIOXIN (TCDD) INDUCTION OF ARYL HYDROCARBON HYDROXYLASE (AHH) ACTIVITY IN A NEW MOUSE ENDOMETRIAL CELL LINE (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:908 1982

Preimplantation mouse embryos exposed in vitro to direct acting carcinogens have been shown to have decreased implantation rates and birth rates. If mouse endometrium has the ability to convert procarcinogens to cytotoxic metabolites or mutagens through activation of microsomal enzymes, exposure of a pregnant mouse to indirect acting procarcinogens can effect implantation and normal development of the fetus. We have isolated a mouse endometrial cell population by mild tryptic digestion of the uterine lining, which shows induction of AHH when TCDD is added to culture for 24 hours. The population of endometrial cells are tetraploid and have been maintained in culture. The cells are adherent to plastic as well as glass and contain numerous large refractile, osmophilic non-membrane-limited granules which are PAS positive but negative when stained with Oil Red O and Alcian Blue. The cells were grown in Dulbeccos modified Eagle's medium (DMEM)-10% fetal calf serum (FCS) with and without estradiol at a concentration of 10-8M and 10-8M. In further experiments, media was changed to DMEM-5% FCS (dextran coated charcoal striped) with and without estradiol. Cell number is increased 1.21 fold after 4 days and 1.45 fold after 6 days in the estradiol treated groups. Cell number is increased 1.32 fold after 4 days in the estradiol treated group grown in striped FCS. Inducibility of AHH activity was investigated by growing cells with and without estradiol and then treating with 0.3nM of TCDD for 24 hours. AHH activity was determined by measuring production of hydroxylated benzo(a)pyrene fluorometrically. Cells grown in the presence of estradiol for 4 days show 11.7 fold induction of AHH activity as opposed to 7.8 fold induction in the cells grown without estradiol. (no Refs)

53. FURTHER CHARACTERIZATION AND APPLICATIONS OF THE 4-CHLOROBIPHENYL HYDROXYLASE ASSAY.

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Adv Exp Med Biol; 136(partA):753-759 1982

In vitro metabolism of 4-chlorobiphenyl (4-CBP) and benzo(a)pyrene (BP) were compared, and indirect evidence that these two chemicals share a common pathway of metabolism is presented. The putative binding of 4-CBP and BP to cytochrome P-450 was examined by room temperature difference spectrophotometry using freshly-prepared microsomes from 1-mo-old male Wistar rats. The apparent spectral dissociation constant (Ksapp) values indicated that cytochrome P-450 bound BP with a greater affinity than 4-CBP. Like the Ksapp values, the apparent Michaelis-Menten constant (Kmapp) values indicated that cytochrome P-450 bound BP more avidly than 4-CBP; the Kmapp values also showed that the binding affinity for both 4-CPB and BP was decreased slightly by phenobarbitone (PB) treatment but increased several-fold by 3-methylcholanthrene (MC) treatment. In noninduced, PB-induced, and MC-induced microsomes, 4-CBP was a competitive inhibitor of BP metabolism and vice-versa. The 4-CBP hydroxylase assay was used to show that 2,2',4,4',5,5'-hexachlorobiphenyl is a PB-type inducer. The 2,2',3,3',4,4'-hexachlorobiphenyl (2,3,4-HCBP) closely resembled a PB-type inducer; however, this isomer was a slightly more potent inducer of BP hydroxylase than PB and was a much more potent inducer of 4-CBP hydroxylase, suggesting that 2,3,4-HCBP has weak MC-type characteristics. The 2,2',3',4,4',5-hexachlorobiphenyl clearly differed from PB and exhibited marked MC-type characteristics, confirming prior reports that the isomer is a mixed (PB + MC)-type inducer. (17 Refs)

54. EFFECTS OF LINDANE TREATMENT ON DRUG METABOLIZING ENZYMES AND LIVER WEIGHT OF CF1 MICE IN WHICH IT EVOKED HEPATOMAS AND IN NON-SUSCEPTIBLE RODENTS.

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Chem Biol Interact; 40(1):1-14 1982

The specific activities of some enzymes which are thought to be involved in the metabolism of lindane were studied in three different mouse strains in order to investigate whether differences exist in the activities of these enzymes. Because the enzyme pattern may change after lindane treatment during the carcinogenicity studies, we also investigated the enzyme activities in animals treated for 3 days or 3 mo with various doses of lindane. The influence of lindane treatment on the relative liver wt was also determined. Basal glutathione-S-transferase activity was higher in males than in females in all three strains, bearing no apparent relationship to susceptibility for tumor formation. However, after treatment with the highest dose of lindane a five- to six-fold induction of this enzyme activity was observed in female CF1 mice, which then together with the male CF1 mice had a higher glutathione-S-transferase activity than untreated and treated B6C3F1 mice and Osborne-Mendel rats. Whether lindane or one of its metabolites is activated by conjugation with glutathione remains to be established. After treatment of the animals with high doses of lindane detergent-treated rat liver microsomes showed a higher UDP-glucuronosyltransferase activity than mouse liver microsomes. This high activity could lead to a rapid conjugation of phenols derived from lindane. The most striking difference observed in this study was the fact that together with the larger increase in absolute and relative liver wt, untreated and treated CF1 mice showed higher monooxygenase activity and, after treatment with lindane, lower expoxide hydrolase activity than rats. Whether the monooxygenase and epoxide hydrolase activities will lead to an accumulation of reactive epoxides derived from lindane remains to be clarified. (18 Refs)

55. TECHNICAL PENTACHLOROPHENOL (PCP-T)-INDUCED SUPPRESSION OF MURINE HUMORAL IMMUNE RESPONSE (MEETING ABSTRACT)

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Toxicologist; 2(1):88 1982

The present studies examined the humoral immune response in mice exposed to 50, 100, 250 or 500 ppm PCP-T in the diet for 9-11 weeks. No overt toxicity was apparent at these exposure levels. The T-cell dependent antiSRBC splenic antibody response was quantitated in Swiss-Webster mice using the Hemolytic Antibody Isotope Release (HAIR) assay. The T-cell independent antiDNP-Ficoll response was quantitated in C57Bl/6 mice by Cunningham's plaque assay. Serum antiDNP antibody levels were measured by passive hemagglutination. Following exposure to 250 or 500 ppm PCP-T, the primary IgM response to SRBC was reduced to 30 and 19% of the control response and the secondary IgM response was delayed by 1 day and suppressed to 54 and 45% of control, respectively. The second IgG response was also delayed 1 day and the peak response suppressed to 82 and 68% of control. Exposure to 50 ppm PCP-T slightly delayed the IgM response but did not affect its magnitude. The IgG response was not altered by 50 ppm PCP-T. A direct suppressive effect of PCP-T on the number of antibody-forming cells (AFC) in the spleen was observed following immunization with DNP-Ficoll. The number of IgM AFC/10(6) spleen cells was reduced to 57, 54, and 33% of control in animals exposed to 50, 100, and 250 ppm PCP-T. In addition, peak serum antibody titers to DNP were delayed and dose dependently suppressed in PCP-T exposed mice. (no Refs)

56. ASSESSMENT OF THE CAPACITY OF 3,3',4,4',5,5'-HEXABROMOBIPHENYL TO SERVE AS A PROMOTER OF HEPATOCARCINOGENESIS (MEETING ABSTRACT)

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Toxicologist; 2(1):99 1982

The objective of this study was to determine if 3,3',4,4',5,5'-hexabromobiphenyl (HBB) can act as a promoter of hepatocarcinogenesis. This congener and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) are similar in that they both cause 3-methylcholanthrene type induction of hepatic microsomal drug-metabolizing enzymes and produce a similar and characteristic pattern of toxic and histologic responses. TCDD has been shown to be a promoter of hepatic cancer in rats. To test the tumor promoting capacity of HBB, female Sprague-Dawley rats weighing 200-250 g were injected ip with diethylnitrosamine (DEN) at a dose of 10 mg/kg 24 hours after a 2/3 partial hepatectomy (PH). Thirty days after PH, groups of 6 rats were fed control diets or diets containing 1 ppm HBB or 500 ppm phenobarbital (Pb). Groups of 3 rats without prior hepatectomy or DEN were fed the same diets. At 6 months, rats were killed and samples were collected for histologic and histochemical evaluation. Gamma glutamyl transpeptidase (GGT) was used to identify enzyme altered foci. The average number of GGT positive foci/cm2 were: control, 0; Pb, 58; HBB, 79. Values for rats not hepatectomized or given DEN were: control, 0; HBB, 11. Rats fed HBB had decreased weight gain and thymic atrophy. Histologically, the liver had severe hepatocellular swelling and vacuolation and focal areas of necrosis. (no Refs)

57. COMPARISON OF THE BINDING PROPERTIES OF CYTOSOLIC RECEPTORS FOR 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) IN VARIOUS MAMMALIAN SPECIES (MEETING ABSTRACT)

Gasiewicz TA, Rucci G
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Toxicologist; 2(1):145 1982

The binding of TCDD and its congeners to a cytosolic receptor protein appears to correlate with their ability to elicit toxic effects in mammals. Differences in species susceptibility to TCDD may be related to alterations in the binding properties of these receptors. Utilizing a hydroxylapatite assay system, we determined the number of receptors, apparent equilibrium dissociation constants (KD), and the ability of TCDD congeners to bind to hepatic and thymic cytosolic receptors from male guinea pigs, rats, hamsters, C57BL/6J, and B6D2F1/J mice. Hepatic receptor concentrations ranged from 23 to 74 fmol/mg cytosolic protein. Those species (guinea pig, rat) which have been found to be most sensitive to TCDD-induced thymic atrophy showed the highest levels of thymic receptors as compared to B6D2F1/J mice and hamsters which showed the lowest levels. In the liver there appeared to be a general relation between receptor affinity towards TCDD and the acute LD50 values in these species. Hepatic receptors from the guinea pig showed the highest affinity while those from B6D2F1/J mice and hamsters demonstrated lower affinities. A similar relationship was observed in the thymus. Also, the ability of various TCDD congeners to bind to hepatic receptors generally decreased with increasing acute LD50 values. (no Refs)

58. EFFECTS OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN ON CULTURED HUMAN EPITHELIAL TARGET CELLS: MODULATION BY HYDROCORTISONE (MEETING ABSTRACT)

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Toxicologist; 2(1):146 1982

TCDD (2,3,7,8-Tetrachlorodibenzo-p-dioxin) is an extraordinarily potent toxin, teratogen and carcinogen. In exposed humans, chloracne, a skin disorder characterized by altered patterns of growth and differentiation in the epidermis and its appendages, is one of the most common clinical findings. In initial studies of the molecular mechanisms of toxicity, several human cell lines derived from squamous cell carcinomas (SCC) of epidermal and oral epithelia have been surveyed for their response to TCDD. The cells were grown in the presence of a lethally irradiated feeder layer of mouse 3T3 cells in Dulbecco-Vogt modified Eagle's medium supplemented with 5% fetal calf serum. Under conditions of clonal growth with continuous exposure to various concentrations of TCDD for 3 wks, colony expansion in the lines SCC 9, 12F2, 12B2 and 13 was inhibited. The ED50 for this response was approximately 0.1 nM, with maximal inhibition at 10 nM. Similar values were obtained for the induction of cytochrome P1-450 mediated monooxygenase activities in these cells. Addition of hydrocortisone antagonized the inhibitory effect of TCDD with an accompanying shift in the dose-response curves. In two lines (SCC 9 and SCC 13) a dose-related stimulatory response to TCDD was noted in the presence of hydrocortisone. (no Refs)

59. CYTOGENETIC EFFECTS OF PESTICIDES. I. INDUCTION OF MICRONUCLEI IN MOUSE BONE MARROW BY THE INSECTICIDE DURSBAN.

Amer SM, Fahmy MA
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Mutat Res; 101(3):247-255 1982

The induction of micronuclei in murine bone marrow cells by the organophosphorus insecticide Dursban (O,O-diethyl-O-(3,5,6-trichloro-2 pyridyl)phosphorothioate) after ip, po or dermal treatment of random-bred Swiss mice was tested. After ip treatment, the percentage of polychromatic erythrocytes (PE) in bone marrow increased in a dose-dependent fashion, reaching about 30% after injection with a single dose of 30 mg/kg body wt. Single doses did not induce micronuclei. Repeated administration, (15-45 mg/kg body wt), however, affected both the percentage of PE and the percentage of PE with micronuclei. After po treatment for 14 days, 80 ppm dursban had no effect on percentage of PE, while 240 ppm caused a significant increase in the percentage of PE. The various treatments with dursban induced a higher percentage of PE with micronuclei. Po dursban at 120 ppm induced a transient increase in PE after 2-3 wk, with percent of PE returning to normal values thereafter. A high percentage of PE with micronuclei was observed over the entire 10 wk treatment period. Dermal application of dursban induced PE 1 and 14 days after treatment, but no effect on the induction of micronuclei was observed. (15 Refs)

BENZENE DERIVATIVES

60. BENZIL, A SELECTIVE INDUCER AND POTENT IN VITRO ACTIVATOR OF MICROSOMAL EPOXIDE HYDROLASE.

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Dept. Biochemistry, Arrhenius Lab., Univ. Stockholm, Stockholm, Sweden
Adv Exp Med Biol; 136(partA):717-728 1982

Structural requirements and kinetics of epoxide hydrolase (EH) activation in vitro was studied using benzil (BZ) and the activating effect of BZ was compared to that of metyrapone (MP) and chalcone epoxide (CE). If the assay for EH was begun immediately after the addition of BZ, the activation was considerably less than that obtained using preincubation. EH activity was linear for at least 10 min in the presence of BZ after preincubation. Maximal stimulation was observed between pH 7.0-8.0 using microsomes from untreated animals. Activation in the presence of BZ was greatly lowered by detergent triton X-100, and activations by MP and CE were also somewhat decreased. BZ affected both the apparent affinity of EH for styrene oxide as well as the maximal rate of catalysis.

Structural requirements for activation were rather specific. When one of two keto groups in BZ was replaced by a hydroxyl group or a hydrogen, the activation was reduced from greater than 400% to 8% and 98%, respectively. When microsomes were incubated with different combinations of BZ, CE, and MP, in a concentration of 1.6 milliM, the EH activation obtained was always equal to that observed with one of the activators alone. BZ is a more specific inducer of EH than trans-stilbene oxide (TSO). No or little relationship was observed between the structural requirements for induction and activation. EH activity in liver microsomes from animals induced with phenobarbital, 3-methylcholanthrene, 2-acetylaminofluorene, TSO, or BZ could be activated in vitro to the same extent as the activity in control microsomes. (17 Refs)

61. ROLE OF MIXED-FUNCTION OXIDASES IN THE FORMATION OF BIOLOGICAL REACTIVE INTERMEDIATES.

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Dept. Biochemistry, Univ. Surrey Guildford, Surrey, England
Adv Exp Med Biol; 136(partA):23-38 1982

Mixed-function oxidases (MFO) in activation of carcinogens and toxic chemicals, toxicity of oxygen in different species, multiplicity of cytochrome P-450 (CP-450), carcinogenicity of cytochrome P-448 (CP-448), and the role of CP-448 in the formation of reactive intermediates are discussed. CP-450 coupled with superoxide dismutase and catalase has the propensity to convert molecular oxygen into water, thereby removing from the cell the excess of molecular oxygen which might otherwise be converted into singlet oxygen and other reactive and toxic forms of oxygen. CP-450 and MFO in mammalian liver and other tissues are located in the rough and smooth endoplasmic reticulum. The earliest events in malignant cell transformation involve changes in synthesis of glycoproteins by epithelial tissues, resulting in impaired synthesis of mucus, changes in character of the glycocalyx, and changes in lysosomal enzyme structure and function. In studies on the formation of ligand complexes with CP-450 with the reactive carbene intermediate from safrole, the loss of CP-450 activity was observed with emergence of MFO activity characteristic of CP-448. CP-450 and CP-448 show no marked difference in their affinities for substrates but do exhibit major differences in the nature of oxygenated products. Some differences in the catalytic activities of the two cytochromes are presented. Whereas the MFO activity of CP-450 generally leads to the detoxication of environmental chemicals, oxygenation by CP-448 may lead to bay-region oxygenation and to formation of reactive intermediates and proximate carcinogens. CP-448 is characteristic of malignant and neonatal tissue, and is associated with the loss of ribosomes from the endoplasmic reticulum, and with changes in glycoprotein synthesis. (41 Refs)

62. COVALENT BINDING OF METABOLICALLY ACTIVATED HYDROCARBONS TO SPECIFIC MICROSOMAL PROTEINS.

Jergil B, Schelin C, Tunek A
Biochemistry 1, Chemistry Centre, Univ. Lundt, S-220 07 Lundt 7, Sweden
Adv Exp Med Biol; 136(partA):341-348 1982

Binding specificity of benzene (BZ), chlorobenzene (CB), 3-methylcholanthrene (MCH), and benzo(a)pyrene (BP) to rat liver microsomal proteins (MP) after metabolic activation was examined. The examined compounds bound covalently to MP in a NADPH-dependent manner indicating that metabolic activation was required for binding. Reduced glutathione inhibited binding. The binding patterns to MP examined by SDS-polyacrylamide gel electrophoresis and fluorography were quite similar for metabolic activated BZ, CB, and phenol. The binding patterns to liver microsomes from phenobarbital (PB)- or MCH-treated rats did not differ significantly from those of control animals. The binding patterns for BP and MCH were distinctly different from those of BZ, phenol, and CB. The binding of these compounds to microsomes from MCH-treated rats was much higher than that to microsomes from control or PB-treated animals. Seven BP metabolites were isolated and incubated with NADPH and microsomes from control or pretreated rats. All isolated metabolites, including BP-4,5-oxide, had to be metabolically activated to bind covalently. Variations were found among the metabolites in extent and specificity of binding. Of the isolated metabolites tested, BP-7,8-dihydrodiol bound most efficiently after metabolic activation, particularly to microsomes from MCH-treated rats. Results suggested that the binding pattern, at least in part, is determined by the mechanism of metabolic activation. (13 Refs)

63. THE CYTOCHROME P-450-MEDIATED METABOLISM OF BIPHENYL AND THE 4-HALOBIPHENYLS.

Parkinson A, Safe S
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Adv Exp Med Biol; 136(partA):745-752 1982

Effects of phenobarbitone (PB) and 3-methylcholanthrene (MC) on the metabolite profiles and overall rates of metabolism in vitro of 4-fluorobiphenyl (4FBP), 4-chlorobiphenyl (4CBP), 4-bromobiphenyl (4-BBP), and 4-iodobiphenyl (4-IBP) was reported. Also, the spectrally-apparent interaction of biphenyl (BP) and the 4-halobiphenyls with noninduced, PB-induced, and MC-induced rat hepatic microsomes was reported. Putative binding of BP and the 4-halophenyls to cytochrome P-450 was examined by room temperature difference spectrophotometry using freshly-prepared microsomes. The liver microsomes were prepared from 1-mo-old male Wistar rats. The rate of metabolism of BP, 4-FBP, and 4-BBP was increased 2x by PB and 4-6x by MC treatment. The rate of metabolism of 4-CBP and 4-IBP was not significantly increased by PB treatment but was increased by more than an order of magnitude by MC treatment. Both the magnitude of the absorbance change and the apparent binding affinity of cytochrome P-450 for BP and the 4-halobiphenyls increased with increasing substrate lipophilicity. The spectrally-apparent interactions failed to indicate any preferential binding of the substrates to either noninduced, PB-induced, or MC-induced microsomes. Thus, the reason for the differential effects exerted by the halogens remains unknown. (13 Refs)

64. REACTION OF MICROSOMAL AND CYTOSOLIC ENZYMES WITH N-ARYLACETOHYDROXAMIC ACIDS IN THE PRESENCE OF OXYGEN.

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Adv Exp Med Biol; 136(partB):951-970 1982

Experiments on the metabolic fate of N-hydroxy-4-chloroacetanilide (N-OH-4ClAA), N-hydroxy-2-acetylaminofluorene (N-OH-2AAF), N-hydroxy-4-acetylaminobiphenyl (N-OH-4AAB), and N-hydroxyphenacetin (NHP) in rabbit or rat liver microsomal and cytosolic systems are reviewed. Differences in substrate affinity cause microsomal and cytosolic N-OH-2AAF, N-OH-4AAB, N-OH-4ClAA, and NHP to be N-deacylated at different rates, but the differences are not clear-cut enough to permit differentiation between carcinogenic polycyclic and noncarcinogenic monocyclic compounds. Differences in the rates of oxidation of the corresponding arylhydroxyamines were also detected, but these were likewise not clear enough for separation of respective poly- and monocyclic compounds. Clear differences in reactivity between poly- and monocyclic nitrosoarenes were observed, but have not been related to toxicity of the corresponding N-arylacetohydroxamic acids. The prominent reactivity of N-OH-2AAF and of 2-nitrosofluorene suggests that the primary lesion, from which tumor growth is initiated, may be caused by this arylhydroxylamine and/or its N-arylacetohydroxamic acid. (38 Refs)

DRUGS, COSMETICS, DETERGENTS AND OTHER COMMERCIAL MATERIALS

65. CALMODULIN, ACTIVATED CYCLIC NUCLEOTIDE PHOSPHODIESTERASE, MICROTUBULES, AND VINCA ALKALOIDS.

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Fed Proc; 41(7):2292-2299 1982

Calmodulin, 1.8 and 10.6 uM, inhibited the polymerization of bovine brain microtubules by 30 and 50%, respectively. Two 55,000-to 68,000-dalton calmodulin-binding proteins as well as calmodulin-dependent and -independent phosphodiesterases (PDE) were found associated with microtubule proteins. Among the antimicrotubule drugs, such as colchicine, podophyllotoxin, griseofulvin, and vinca alkaloids (vinblastine, desacetylvinblastine amide, and vincristine), the vinca alkaloids were selective inhibitors of calmodulin-activated PDE activity. This action of vinca alkaloids resides in the catharanthine moiety of vinblastine molecule. An alpha2 inhibitor, yohimbine, affects the microtubules, and a series of alpha-adrenoceptor blocking agents were examined for their effects on calmodulin-dependent PDE. The relative order of the potency is phenoxybenzamine = dibenamine greater than phentolamine greater than yohimbine greater than prazosin greater than tolazoline, and the first four drugs in this series were selective inhibitors of calmodulin action. Inasmuch as phenoxybenzamine and dibenamine are alkylating agents, the effects of antineoplastic alkylating agents on the calmodulin action were also examined. Busulphan, melphalan, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, and streptozotocin (up to 4 mM) were not selective inhibitors of calmodulin action. Maytanisine, a vinca alkaloid-type antimicrotubule agent as well as an alkylating agent, selectively inhibited the calmodulin with a potency similar to vincristine. In addition, phenoxybenzamine affected Ca++-dependent fluorescence induced by the interaction between calmodulin and hydrophobic fluorescent probes, whereas vinblastine was ineffective. However, the binding of vinblastine to calmodulin is calcium dependent. Studies such as these suggest the importance of physical and structural considerations in drugs binding to calmodulin was well as at least two different binding sites for drugs on calmodulin. (Author abstract) (52 Refs)

66. RENAL AND HAEMOPOIETIC PROLIFERATIVE DEFECTS AS A DELAYED CONSEQUENCE OF CIS-PLATIN, ADRIAMYCIN AND DAUNOMYCIN TREATMENTS.

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Br J Cancer; 45(3):421-428 1982

The long-term effects of Adriamycin (ADR), daunomycin (DMN) and cis-dichlorodiammine platinum (II) (DDP) on the ability of murine renal tubular epithelium and erythropoiesis to respond to an acute proliferative stress was investigated. Folic acid (FA) and acute anemia induced by bleeding were used as acute proliferative stimuli for renal-tubule epithelium and erythropoiesis respectively. The ability of these normal cell-renewal systems to mount a regenerative proliferative response was evaluated by radioisotopic, morphological and gravimetric techniques 4 months after drug treatment. The results indicate that pretreatment with these agents produce a long-lasting reduction in the ability of these cell-renewal systems to mount regenerative proliferation. In the kidney, the ability to respond to FA was most severely compromised by ADR and DDP, whereas in the erythropoietic system all three agents induced a long-lasting proliferative defect. (Author abstract) (35 Refs)

67. ROLE OF GLUTATHIONE IN LIVER-MEDIATED MUTAGENICITY OF ACRYLONITRILE.

Duverger-van Bogaert M, Lambotte-Vandepaer M, De Meester C, Mercier M, Poncelet F
Laboratoire de Toxicologie et Bromatologie, UCL-72, 37, Avenue E. Mounier 27, B-1200 Brussels, Belgium
Toxicol Lett; 11(3/4):305-311 1982

The mutagenic activity of acrylonitrile (ACN) was studied in Salmonella typhimurium strain TA 1530 after exposure to microsomes, cytosolic fractions and postmitochondrial fractions from untreated and phenobarbitone pretreated rats and mice. Glutathione (GSH), important in biotransformation of ACN, when added to the activation system, increased the mutagenic response. The adduct between ACN and GSH was not mutagenic. (25 Refs)

68. STUDIES IN THE INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN DROSOPHILA MELANOGASTER BY NITROHETEROCYCLIC COMPOUNDS.

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Mutat Res; 101(3):209-236 1982

The induction of sex-linked recessive lethals in Drosophila melanogaster by 24 hr nitroheterocyclic compounds was investigated. The adult feeding technique was used in most cases, and injection and larval feeding in others. Of the nitroimidazoles tested, toxicity increased in the order metronidazole, nimorazole, ronidazole, dimetridazole. Among the nitrofurans, only nitrovin, furazolidone, and furaltadone were clearly mutagenic. Nitrofurantoin and niridazole were ambiguous. Nitrofurans were active at lower molar concentrations than were nitroimidazoles. 4-Nitroquinoline oxide was clearly mutagenic when fed to larvae. Drosophila gut flora were shown not to play role in the activation of ZK 26.173 and furazolidine to mutagenic metabolites. Activation of ZK 26.173 was significantly inhibited in Drosophila strains lacking xanthine dehydrogenase and aldehyde oxidase. (72 Refs)

69. MUTAGENICITY SCREENING OF TWENTY-FIVE COSMETIC INGREDIENTS WITH THE SALMONELLA/MICROSOME TEST.

Blevins RD, Taylor DE
Div. Health Sciences, East Tennessee State Univ., Box 22690-A, Johnson City, TN, 37614
J Environ Sci Health [A]; 17(2):217-239 1982

Nine of 25 cosmetic ingredients tested demonstrated potential mutagenicity in the qualitative spot test in Salmonella histidine auxotrophs. Only one of the nine ingredients, DEA laureth sulfate, gave a dose-related 4.3-fold increase in colony counts in the plate incorporation test at the highest non-inhibitory dose with strain TA98 and no S9 mix. (33 Refs)

70. 16ALPHA-[77BR]BROMOESTRADIOL: DOSIMETRY AND PRELIMINARY CLINICAL STUDIES.

McElvany KD, Katzenellenbogen JA, Shafer KE, Siegel BA, Senderoff SG, Welch MJ, Los Alamos Medical Radioisotope Group
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J Nucl Med; 23(5):425-430 1982

An estrogen-receptor-binding radiopharmaceutical, 16alpha-[77Br]bromoestradiol-17beta, has been used successfully at high specific activity to image carcinogen-induced mammary tumors in rats and in preliminary studies to image breast tumors in patients. The biodistribution of the labeled estrogen in rats and its clearance in a monkey were used to estimate the radiation absorbed doses to a human resulting from administration of the radiopharmaceutical. Preliminary imaging studies in patients with mammary carcinoma show promising results and warrant further development of radiolabeled estrogens, particularly those carrying positron emitters that could permit positron emission tomography - for example Br-75 or F-18. (Author abstract) (23 Refs)

71. ANALYSIS OF MITOMYCIN C BIOREDUCTION ALKYLATION PRODUCTS BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (MEETING ABSTRACT)

Andrews PA, Pan SS, Bachur NR
Baltimore Cancer Research Program, NCI, NIH, Baltimore, MD, 21201
Proc Am Assoc Cancer Res; 23:815 1982

Mitomycin C (MC) and 9 derivatives were resolved by reversed-phase high performance liquid chromatography. The column used was a 10 cm x 8.0 mm C18 (10u) radial compression cartridge fitted with a 7 cm x 2.1 mm guard column packed with CO:PELL ODS. Compounds were eluted with a 13 minute linear gradient from 100% potassium phosphate (0.01M, pH 7.0) to 50% phosphate, 50% methanol at a flow rate of 3.0 ml/min. Peaks were detected at 365 nm and 313 nm. Cis-and-trans-2,7-diamino-1-hydroxymitosene (k'14.4 and 11.7) were generated by acidic hydrolysis of MC (k'12.7). These isomers were purified on a 50 cm x 9.4 mm M9 ODS-3 semi-preparative column and treated with acetic anhydride/pyridine. Electron ionization mass spectroscopy confirmed their identities. Catalytic hydrogenation of MC generated 2,7-diaminomitosene (k'16.6). Purification, acetylation and mass spectral analysis confirmed its identity. Alkylation reactions of MC at pH 3.5 produced 4 peaks (k'3.1, 4.1, 6.5, 7.1) dependent on phosphate concentration. All seven of the above compounds had absorbance spectra typical of 7-aminomitosene. Two additional minor peaks (k'13.4, 17.7) were detected that had absorbance spectra similar to 2-amino-1,7-dihydroxymitosene. NADPH cytochrome P450 reductase and xanthine oxidase readily metabolize MC anaerobically in the presence of electron donors. Nine metabolites were detected that co-chromatographed with the chemically generated species. Cis- and-trans-2,7-diamino-1-hydroxymitosene were conclusively verified in these incubations by mass spectroscopy following purification and acetylation. Besides the reactive center expressed at C1 following bioreduction, a second reactive center expressed at C7 is implicated by these results. (no Refs)

72. MUTAGENICITY, CARCINOGENICITY, AND BIOCHEMICAL ACTIVITY OF ELEVEN NEW 5-NITROFURAN ANALOGS (MEETING ABSTRACT)

Erturk E, Swaminathan S, Ichikawa M, Bryan GT
University of Wisconsin Center for Health Sciences, Madison, WI, 53792
Fed Proc; 41(3):330 1982

New analogs of the bladder carcinogen N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide, (FANFT), were synthesized and tested for antibacterial activity against Esherichia coli and Staphylococcus aureus, and for mutagenicity against Salmonella TA-100 (Ames test). Two compounds were further tested for their ability to induce ornithine decarboxylase (ODC) in the urinary bladder, and for their carcinogenicity in female rats after 46 wks of exposure in diet followed by 20 wks of control feed. The test compounds were: 2-formylamino-4-[2-(5-nitro-2-furyl)vinyl]-1,3-thiazole (I), 2-amino-4-[2-(5-nitro-2-furyl)vinyl]-1,3-thiazole (II), 5-nitro-3,4-diphenyl-2-methyl furoate (III), 5-hydroxylamino-3,4-diphenyl-2-methyl furoate (IV), 5-amino-3,4-diphenyl-2-methyl furoate (V), methyl(2-oxy-3,4-diphenyl-4-cyano)butanoate (VI), methyl(2-oxy-3,4-diphenyl-4-cyano)butenoate (VII), 2,5-dioxy-3,4-diphenyl-3-pyrroline (VIII), 5-(N-acetylamino)-3,4-diphenyl-2-methyl furoate (IX), 5-(N,N-diacetylamino)-3,4-diphenyl-2-methyl furoate (X), and 5-(N-acetylamino)-2-(2-thiazolyl) furane (XI). I and II, the vinyl bridged analogs of FANFT, showed antibacterial activity against both bacteria, were mutagenic to TA-100, and induced urinary bladder ODC; however, they were not carcinogenic in rats. III was antibacterial and mutagenic, and other analogs were neither antibacterial nor mutagenic. (no Refs)

73. CHARACTERIZATION OF A LYMPHOMA INDUCED BY BUSULFAN AND CHLORAMPHENICOL IN CAF1 MICE (MEETING ABSTRACT)

Bhoopalam N, Dalidowitz J
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Fed Proc; 41(3):410 1982

We previously showed that injection of Busulfan and chloramphenicol into CAF1 mice induced the development of T-cell lymphoma in 50% of mice. The lymphoma cells were transplantable into other CAF1 mice by subcutaneous injections. In the recipients the leukemic cells grew as a subcutaneous nodule with late infiltration of the spleen. The cells from the nodule expressed Thy 1.2 alloantigen, brain associated antigen on 90% and Lyt 2.2 antigens 58% of the cells. They were negative for Lyt 1.1, 2.1, 1.2 and Ia antigens. The primary immune response to sheep erythrocytes were measured in these mice by hemolytic plaque assay. The sheep cell immune response was normal when compared to age matched control, but depended on the state of the splenic infiltration. The complete infiltration of the spleen diminished the response but with partial infiltration the response was intact. The cells from the nodule were negative for plaque forming cells. These studies indicate that the lymphoma induced by Busulfan and chloramphenicol are transformed T cells which did not interfere with primary sheep cell immune response in the lymphoma mice. (no Refs)

74. THE EFFECT OF CIS-DIAMMINEDICHLOROPLATINUM (II) ON IMMUNE FUNCTION IN VITRO AND IN VIVO.

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Cancer Immunol Immunother; 12(3):191-196 1982

Effects of cis-diamminedichlorplatinum(II) (cis-DDP) on a naturally occurring immune function, spontaneous monocyte-mediated cytotoxicity (SMMC) are reviewed. Cis-DDP selectively inhibits DNA rather than RNA or protein synthesis in eukaryotic and prokaryotic cells. Cis-DDP is mutagenic, teratogenic, and carcinogenic; and it can induce lysogenic DNA viruses to lyse their host cells. In vitro treatment of human mononuclear cells with concentrations of cis-DDP as low as 10(-9) M for 15 min will enhance SMMC. Cis-DDP specifically and selectively stimulated the monocyte killer itself rather than inhibiting the lymphocyte suppressor function. Thus, at a concentration 1,000-fold lower than that needed to create detectable DNA damage or produce cytotoxic effects in cultured malignant cells, cis-DDP stimulated a naturally-occurring immune function. Eight patients with ovarian cancer were studied and their SMMC prior to successive courses of chemotherapy was sequentially determined. In each of the seven evaluable patients their cytotoxic function increased three-fold during combination chemotherapy that contained cis-DDP as one agent. Six of these seven patients responded with measurable tumor regression. Data indicated that cis-DDP has a direct tumoricidal action and enhances a naturally occurring immune function causing destruction of tumor by the host's own activated defense system. Normal peripheral mononuclear leukocytes were treated with 10(-5) M cis-DDP for 1 hr and then the ability of these cells to respond to various mitogens (phytohemagglutinin, concanavalin A, pokeweed mitogen) and specific antigens (tetanus, diphtheria) was assayed by measuring their 3H-thymidine incorporation during the terminal 4 hr of the 3-or 6-day assay. No difference was observed in the ability of the cis-DDP-treated cells to respond to the mitogens or antigens. (50 Refs)

75. OXIDATIVE METABOLISM OF THE SYNTHETIC ESTROGENS HEXESTROL AND DIENESTROL INDICATES REACTIVE INTERMEDIATES.

Metzler M, McLachlan JA
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Adv Exp Med Biol; 136(partA):829-837 1982

Oxidative metabolism of meso-hexestrol (HES) and alpha-dienestrol (E,E-DIES) was studied in rats to determine whether electrophilic intermediates are formed from these estrogens. Chemical structures of HES metabolites in the glucuronide fraction in HES-treated rats are presented. For two of the metabolites, 1-hydroxy-HES and 3'-hydroxy-HES, authentic reference compounds were available to confirm their structure. Metabolic fate of HES comprises hydroxylation at the aromatic rings followed by methylation, hydroxylation at the terminal methyl group of the hexane chain, and combinations of these metabolic steps. No indication for the conversion of HES into diethylstilbestrol was found. When the biliary glucuronides of E,E-DIES-treated rats were analyzed, the predominant compound was unchanged E,E-DIES. Three major metabolite peaks in the gas chromatogram had mass spectra indicative for the formation of an olefinic epoxide; one peak could represent the epoxide itself, while the other two peaks might denote rearrangement products. The oxidative biotransformation of E,E-DIES appears to involve olefinic epoxidation in addition to catechol formation, although the extent of metabolic oxidation of E,E-DIES is rather low as compared to HES. (11 Refs)

76. OCCURRENCE OF BROMINATED ALKYLPHENOL POLYETHOXY CARBOXYLATES IN MUTAGENIC WASTEWATER CONCENTRATES.

Reinhard M, Goodman N, Mortelmans KE
Environmental Engineering and Science, Dept. Civil Engineering, Stanford Univ., Stanford, CA, 94305
Environ Sci Technol; 16(6):351-362 1982

Mutagenicity data obtained during a 1.5 yr study on effluents from the Orange County, Southern California, Water Factory 21 (WF21) were presented. Mutagenic activity was determined with Salmonella typhimurium strain TA100. Organics were concentrated by adsorption on Amberlite XAD-8 ion-exchange resins, ultrafiltration, and gaseous purging. Direct mutagenicity was detected only in the concentrates from XAD-8; in all other concentrates, the response was negative. Samples were up to 1 gallon in size. The data from the XAD-8 concentrates were emphasized and the chemical characterization of the mutagenic extracts was discussed. The activity of direct acting mutagens appeared to increase at the recarbonation stage, where 6-10 mg/liter of chlorine was added. Subsequent activated carbon treatment removed activity effectively. Final chlorination typically with 25 mg/liter of chlorine led to the reoccurrence of mutagenicity. Mutagenicity was found in organic fractions primarily containing carboxylic acids including brominated and nonbrominated alkylphenol polyethoxy carboxylic acids (BrAPEC and NBrAPEC). Potential mutagenicity of the BrAPEC was suggested, but preliminary experiments failed to confirm this hypothesis. (45 Refs)

77. MUTAGENIC, CARCINOGENIC AND TERATOGENIC EFFECTS OF STYRENE.

Sram RJ, Pohlova H, Topinkova E
Klinika hygieny a epidemiologie, Srobarova 48, 100 42 Prague 10, Czechoslovakia
Prac Lek; 34(2):68-72 1982

Studies on the mutagenic, carcinogenic and teratogenic properties of styrene are reviewed. Styrene was found to be mutagenic and teratogenic in experimental animals and humans and carcinogenic in experimental animals (inducing pulmonary adenoma and adenocarcinoma, as well as hepatocellular carcinoma in mice). Epidemiological studies failed to demonstrate the increased mortality due to malignant tumors among subjects exposed to styrene. Increased frequency of aberrant peripheral lymphocytes was found in workers exposed to styrene. (46 Refs) (In CZE)

REVIEWS AND OTHER COMPOUNDS

78. EXPERIMENTAL TUMORS OF THE PERIPHERAL NERVOUS SYSTEM.

Beniashvili DS
Cancer Res. Center, Thilisi, USSR
Eksp Onkol; 4(2):12-19 1982

Incidence of spontaneous and induced tumors of the peripheral nervous system (PNS) in the experimental animals is reviewed. PNS neoplasms were induced after sc or im applications of polycyclic hydrocarbons. Injection of methylcholanthrene into the sciatic nerve produced tumors in rabbits and in random-bred rats. The spectrum of nitrosamine-induced PNS tumors was shown to depend upon the animal species, age, strain, dose, and the mode of administration. Prolonged iv administration of methylnitrosourea (MNU) resulted in selective induction of CNS and PNS tumors. High incidence of neurogenic tumors was recorded in Fisher and BD-IX rats. Ethylnitrosourea (ENU) showed high affinity to PNS during transplacental carcinogenesis. Sensitivity of rat embryo to ENU was 30-50x greater than that of the adult rats. The highest incidence of PNS tumors was observed after ENU administration during the last third of the gestation. Nitroso compounds and urethane were reported to induce tumors of the sympathetic nervous system in rabbits, hamsters, and rats. (103 Refs) (In RUS)

79. CURRENT CONCEPTS OF THE ETIOLOGY AND PATHOGENESIS OF LUNG CANCER.

Chaklin AV, Gritsiute LA
No affiliation given
Vopr Onkol; 28(2):3-9 1982

Literature data on the role of smoking and environmental pollutants in the etiology of lung cancer (LC) are reviewed. Epidemiological studies showed the relationship between the smoking and incidence of LC. LC morbidity in 45-64 yr old men increased from 1.4 per 100,000 for nonsmokers to 5.9 for those who smoked 5 cigarettes/day, 13.5 for those who smoked 6-16 cigarettes/day, 29.5 for those who smoked 25-56 cigarettes/day, and 47.4 for those who smoked greater than 56 cigarettes/day. Carcinogenicity of tobacco tar is associated with the presence of polycyclic hydrocarbons, N-nitrosamines, vinyl chloride, phenols, and various co-carcinogens. Recent studies showed the carcinogenic effect of 'passive' smoking. Increased LC morbidity in the regions with intensive chemical industry indicates the co-carcinogenic effect of such air pollutants as sulfur dioxide. Pathogenesis of LC is associated with the history of chronic lung inflammation, tuberculosis, scleroderma, exposure to asbestos, immunologic suppression, and individual activity of aryl hydroxylase. (45 Refs) (In RUS)

80. PROPHYLAXIS OF LUNG CANCER.

Napalkov NP
No affiliation given
Vopr Onkol; 28(2):10-15 1982

Approaches to lung cancer (LC) prevention are outlined, with special emphasis on the role of environmental and occupational pollutants in the etiology and pathogenesis of LC. The increase of LC morbidity is associated with significant growth and development of chemical industry. Following factors were shown to play a role in the etiology of LC: arsenic and its derivatives, chromium and its derivatives, industrial purification of nickel, hematite mining, asbestos, bis-chloromethyl ether, mustard gas, pyrolysis products, and ionizing radiation. The risk of LC was directly related to the cigarette consumption. The carcinogenic effect of cigarette smoke was shown in the animal experiments. Post-mortem examination of smokers showed marked metaplastic changes in the bronchi. It was suggested that LC control and prevention should include active anti-smoking campaign, follow-up of the patients with precancerous chronic lung diseases, and ban on production and use of industrial carcinogens. (18 Refs) (In RUS)

81. MUTAGENICITY OF PYROLYSATES FROM GUANIDINE, UREIDE, SECONDARY AMINES AND POLYAMINES FOUND BY THE SALMONELLA/ MAMMALIAN-MICROSOME TEST.

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Mutat Res; 101(3):175-187 1982

The mutagenicity of pyrolysates formed from various nitrogenous compounds at 300, 400, 500 and 600 C were assayed in the Salmonella/mammalian-microsome test. Compounds subjected to pyrolysis included guanidine, ureide, and a variety of secondary and polyamines. Pyrolysates from methylguanidine, agmatine, dihydrouracil, dimethylamine, diethylamine, trimethylamine, triethylamine, pyrrolidine, morpholine, sarcosine, piperazine, piperidine, spermine and spermidine were found to be mutagenic. Mutagenicity began to be evident for pyrolysates obtained at temperatures 400-600 C (was highest for 600 C-except for that derived from methyl-guanidine) when S-9 mixture was added. Pyrolysates from morpholine, piperazine, piperidine, spermine and spermidine were toxic for TA98 and TA 100, while those from dimethylamine and diethylamine were toxic for TA98. The pyrolysate from proline had the highest mutagenic activity, on both TA 98 and TA 100, (with metabolic activation). With metabolic activation, the number of revertants of TA 98 induced by the pyrolysates was greater than those of TA 100. Pyrolysates from dimethylamine, diethylamine and pyrrolidine were slightly mutagenic toward TA 100 in the absence of microsomal activation. (44 Refs)

82. EFFECT OF MALONALDEHYDE AND ACETALDEHYDE ON CULTURED MAMMALIAN CELLS. PRODUCTION OF MICRONUCLEI AND CHROMOSOMAL ABERRATIONS.

Bird RP, Draper HH, Basrur PK
Dept. Nutrition, Univ. Guelph, Guelph, Ontario N1G2W1, Canada
Mutat Res; 101(3):237-246 1982

The genotoxic effects of malonaldehyde (MA) and acetaldehyde (AA) were investigated using rat skin fibroblasts grown in primary culture. Production of micronuclei and aberrant chromosomes were used as indices of genotoxicity. Micronuclei were observed in cultures exposed to all concentrations of MA tested, this effect being concentration-dependent at least up to 10(-3) M. AA treatment also resulted in dose-dependent production of micronuclei, although higher concentrations were required. Treatment of the cells with MA at 10(-4) or 10(-3) M for 12 hr resulted in structural aberrations in the chromosomes, including acentric chromosomal fragments, achromatic lesions and chromatid breaks. In the case of AA, only 10(-3) M concentration produced an increase in metaphases with chromosomal aberrations. The effect of 10(-3) M AA was similar to that of 10(-4) M MA. Treatment with either aldehyde at either concentration resulted in a marked increase in the number of metaphases with structural and numerical aberrations. MA at all concentrations tested induced chromatid breaks, gaps, deletions and fragmentation. AA produced similar abnormalities but only at the higher concentration. (30 Refs)

83. INDUCTION OF PROLACTIN-DEFICIENT VARIANTS OF GH3 RAT PITUITARY TUMOR CELLS BY ETHYL METHANESULFONATE: REVERSION BY 5-AZACYTIDINE, A DNA METHYLATION INHIBITOR.

Ivarie RD, Morris JA
Dept. Molecular and Population Genetics, Univ. Georgia, Athens, GA, 30602
Proc Natl Acad Sci USA; 79(9):2967-2970 1982

GH3 cells are a rat pituitary tumor line expressing two pituitary peptide hormones, prolactin (rPRL) and growth hormone. Recently, it was found that the DNA alkylating agent ethyl methanesulfonate can induce the appearance of rPRL-deficient GH3 cell variants at a high frequency (ca 20-30%). As shown here, such variants cannot be induced at high frequency by irradiation of wild-type GH3 cells with ultraviolet light, indicating that the effect may be specific to treatment with alkylating agents. Furthermore, the DNA methylation inhibitor 5-azacytidine reverted an ethyl methanesulfonate-induced rPRL-deficient variant into rPRL-expressing cells at high frequency (ca 50%). The revertants were stable for at least 30-35 generations. These results support the hypothesis that the alkylating agent may promote the specific methylation of the rPRL gene or a gene regulating its activity, either one of which leads to inactivation of expression of the rPRL gene in GH3 cells. (Author abstract) (52 Refs)

84. FATE OF EPOXIDES.

Oesch F
Inst. Pharmacology, Univ. Mainz, D-6500 Mainz, W. Germany
Adv Exp Med Biol; 136(partA):39-52 1982

Structure-activity relationships for the mutagenicity of a series of closely related epoxides are described and control of reactive metabolites derived from closely related aromatic compounds by different enzymes is discussed. The mutagenicity of a homogenous series of 17 epoxides was studied using four tester strains of Salmonella typhimurium. In strains TA 100 and TA 1535, which are base-pair substitution mutants, 12 of the epoxides were detected as mutagens. A number of structurally similar 1,2-disubstituted oxyranes, which occur as structural units in a wide variety of drugs and natural compounds, are weak or moderate mutagens. The presence of the double bond in formal conjugation with the epoxide ring increased the mutagenicity relative to the saturated oxyrane. The mutagenicity of benz[a]anthracene investigated in the mammalian enzyme mediated Salmonella test was affected very differently by the same modifications of the metabolizing system, in spite of very similar chemical structures and physicochemical properties of the compounds studied. Microsomal epoxide hydrolase activity in different species towards three different substrates is presented. Epoxides are electrophilic reactive to varying degrees and can chemically react with nucleophilic tissue constituents thereby altering critical cellular macromolecules including DNA, RNA, and proteins. Non-enzymic rearrangement and several enzyme-catalyzed reactions compete with this covalent binding. (34 Refs)

85. PATHOLOGY.

Goyer RA
Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC
JAMA; 247(21):2973-2975 1982

Recent results concerning the relationship between toxic chemicals and cancer are reviewed. Linking toxin exposure to disease often requires information beyond that obtained in a pathological examination. Asbestos and formaldehyde are two materials that are of particular interest due to their widespread use and carcinogenicity. Recent incidents relating exposure to chlordecone and dibromochloropropane with infertility have stimulated concern about the testis as a target organ for toxicity. (15 Refs)

86. HOST AND ENVIRONMENTAL FACTORS ENHANCING CARCINOGENESIS IN THE RESPIRATORY TRACT.

Nettesheim P, Topping DC, Jamasbi R
Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709
Annu Rev Pharmacol Toxicol; 21:133-163 1981

Selected laboratory studies conducted during the last decade that exemplify what has been learned about the multicomponent etiology of lung cancer are reviewed. Sections concerning experiments relating to modification of host susceptibility include the following: studies on age specific susceptibility of respiratory tract epithelium to carcinogens, effect of immune suppression on the development of respiratory tract tumors, role of dietary vitamin A in the susceptibility to lung cancer induction, and role of respiratory tract infections in the pathogenesis of lung cancer. Sections concerning the interaction of environmental or occupational agents include: two stage carcinogenesis in respiratory tract epithelium, cocarcinogenic effects of chrysotile asbestos, role of so-called inert particles in respiratory tract carcinogenesis, nickel subsulfide as a possible cocarcinogen in occupational lung cancer, studies on benzo(e)pyrene as a cocarcinogen, and role of irritant gases and vapors as cocarcinogens in the respiratory tract. (117 Refs)

87. SELENIUM, ESTRADIOL 17BETA, NITRITES, AND HUMAN BREAST CANCER.

Lombard LF
11145 Northborough Lane, Richmond, VA, 23235
Med Hypotheses; 8(4):371-382 1982

An hypothesis postulating an etiology of breast cancer from interactions among selenium, estradiol 17beta, nitrites, and RBC is presented. In this hypothesis, in the presence of nitrites, triglycerides, and selenium, estradiol 17beta is catalyzed by an unknown enzyme (' X') to form the known carcinogen chrysene, which is complexed with methemoglobin in the RBC. The conversion process may partially take place in the gastrointestinal tract and liver, with more direct conversion in breast cells after transport. Chrysene, in the breast cells, already under attack by nitrites or lysosomal enzymes, causes additional focal hyperplasia, metaplasia, neoplasia, anaplasia, gene alteration, and carcinoma. The process may also require high androgen levels and other trace elements, such as zinc. (51 Refs)

88. CARCINOGENICITY OF CHLORINATION BY-PRODUCTS: TRIHALOMETHANES.

Pereira MA

Health Effects Res. Lab., Cincinnati, OH

Carcinogenicity of Chlorination By-Products: Trihalomethanes. Available from National Technical Information Service, Springfield, VA, as PB82-131855:, 28 pp., 1981.

There is insufficient evidence to indicate anything but the weakest, if any, tumor initiating activity for trihalomethanes. Chloroform in all the tests other than the low level of DNA binding did not indicate any possible tumor initiating activity. The only indication that the other trihalomethanes are tumor initiators was their marginal mutagenic activity in the Ames Salmonella Assay. The trihalomethanes would appear to possess tumor promoting activity as indicated by (1) induction of regenerative hyperplasia, (2) molecular markers such as induction of ODC and (3) the apparent weak promoting activity of chloroform in the rat liver foci bioassay. The dose-response relationship of the tumor promoting activity of chloroform could possess a threshold as indicated by the induction of ODC and regenerative hyperplasia. Therefore, the wt of the present evidence would indicate that the extrapolation model employed to estimate the low dose carcinogenic response for chloroform should be different than the model used for genotoxic carcinogens. However, it must be emphasized that confirming evidence is required to support this conclusion. (Author abstract)

89. CANCER CAUSING CHEMICALS.

Sax NI, Weisburger EK, Schottenfeld D, Haas J, Feiner B, Castelman BI, Lewis RJ

No affiliation given

Cancer Causing Chemicals. New York, Van Nostrand Reinhold Company, 466 pp., 1981.

Chemical carcinogenesis and its relevance for the general population, carcinogens in the workplace, control of workplace carcinogens, and regulations affecting use of carcinogens are discussed. Approx 25,000 synonyms and cross references to each of the 2,400 basic carcinogens (BC) are listed, described and discussed. Carcinogenicity of each of the BC is rated as 'conclusive', 'suggestive', or 'indeterminate' based upon literature research against criteria applied to this data by means of computer. Smoking, radiation, location or geographic location, drug use, congenital and genetic diseases, congenital defects, familial susceptibility, other diseases increasing the risk of developing neoplastic diseases, precancerous conditions, acquired diseases, and life-style are responsible for much of the general cancer incidence. Principles of non-human testing for chemical carcinogenicity are discussed with respect to the relevance of animal and in vitro studies for predicting human risks. Current concepts of prevention and control of occupational cancers are presented. Process, plant, and equipment design; exhaust ventilation; respiratory protection; protective clothing and personal hygiene; monitoring; and specific control techniques are included in the control of workplace carcinogens. Products and wastes containing carcinogens should be appropriately packed, labeled, and disposed of. The use of recognized carcinogens should be fully justified in terms of their need in society and available alternatives. (312 Refs)

90. METABOLISM OF CHEMICAL CARCINOGENS.

Weisburger JH, Williams G

American Health Foundation, Naylor Dana Inst. for Disease Prevention, Valhalla, NY

Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Chemical carcinogens are defined by their ability to induce tumors. Four types of response have generally been accepted as evidence of tumorigenicity. These include an increased incidence of the tumor types occurring in controls, the occurrence of tumors earlier than in controls, the development of types of tumors not seen in controls, and an increased multiplicity of tumors in individual animals. Examples of the genotoxic carcinogen class include alkylating agents which are activation independent, aromatic amines and polycyclic aromatic hydrocarbons which are activation-dependent, and metals. Examples of the epigenetic carcinogen class include plastics and asbestos, estrogen, androgen, purine analog, and phorbol ester. Promotors are agents that increase the tumorigenic response to a carcinogen when applied after the carcinogen. Genetic factors, sex and endocrine status, age, diet, activities of intestinal flora, the presence of other chemicals, the mode and frequency of exposure, and numerous other factors influence the variation in carcinogen metabolism. Research during the last few decades has pinpointed natural products as major causes of cancer in humans in various parts of the world. (486 Refs)

91. CHEMICAL CARCINOGENESIS: INTERACTIONS OF CARCINOGENS WITH NUCLEIC ACIDS.

Rajalakshmi S, Prema M, Sarma D

Dept. Pathology, Univ. Toronto, Toronto, Ontario, Canada

Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

The nature of modified nucleic acids following interactions with carcinogens is reviewed. Interactions of chemical carcinogens with DNA include covalent interactions such as alkylating agents, nitrosamines and nitrosamides, and noncovalent interactions of both internal and external binding types. Purine-N-oxides and many inorganic metal compounds are known to be carcinogenic. The use of fractionation techniques has revealed that carcinogens exhibit a preferential interaction with some regions of DNA in chromatin. Interactions of chemical carcinogens with RNA have been studied, and alterations in RNA have been attributed to alkylating agents such as nitrosamines and nitrosamides, to urethan, to aromatic amines and amides, and to polycyclic aromatic hydrocarbons. Interactions of carcinogens with nucleic acids exert a profound effect on the structure and synthesis of DNA and RNA, gene expression, and regulation of cellular development. Although the exact mechanism or mechanisms by which DNA damage and repair are involved in carcinogenesis is not completely understood, there is overwhelming evidence indicating a causal relationship between these two processes. (634 Refs)

92. SOME EFFECTS OF CARCINOGENS ON CELL ORGANELLES.

Svoboda DJ, Reddy J

Dept. Pathology and Oncology, Univ. Kansas Coll. Health Sciences, Kansas City, KS

Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Several observations regarding effects of carcinogens on cell ultrastructure published from 1972 through 1979 are reviewed. Carcinogens whose effect on cell organelles have been studied include the aflatoxins, diethylnitrosamine, dimethylnitrosamine, ethionine, pyrrolizidine, alkaloids, tannic acid, and thioacetamide. Changes caused by carcinogens include nuclear enlargement, increase in the number of nucleoli, conspicuous lysosomes, increase in the smooth endoplasmic reticulum (SER), detachment of ribosomes from the rough endoplasmic reticulum, zonal or diffuse decrease in glycogen, mitochondrial swelling, and a redistribution in the fibrillar and granular components of the nucleus. Most of the carcinogens, in the doses administered, caused slight to moderate necrosis and variable degrees of inflammatory infiltrate. In chronic studies, most of the carcinogens caused alterations either in the proportion or configuration of nucleolar components. There was an increase in interchromatin and perichromatin granules with ethionine and enlargement of interchromatinic spaces with thioacetamide. The most consistent cytoplasmic changes were increased SER and detachment of ribosomes from ergastoplasmic membranes. (210 Refs)

93. SEQUENTIAL ASPECTS OF CHEMICAL CARCINOGENESIS: SKIN.

Berenblum I

Weizmann Inst. Science, Rehovot, Israel

Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

The two-stage hypothesis, the initiation-promotion hypothesis, was based on animal studies of sequential stages of skin carcinogenesis. Initiators for skin carcinogenesis include 2-acetylaminofluorene, UV light, beta-radiation, certain metabolites of 'complete' carcinogens, various alkylating agents and mutagens. Promoters for skin carcinogenesis include physical agents, 'complete' chemical carcinogens, non- or weakly-acting skin carcinogens, croton oil, straight-chain N-alkanes, phenolic compounds, extracts of tobacco leaf, and extracts of tobacco smoke condensates. The two-stage system in skin carcinogenesis has been extended, based on further experiments. Evidence that a mutational change in the DNA genome was responsible for the initiating change of carcinogenesis is based on the ability of most carcinogens to bind with DNA and that there is a fairly good correlation between mutagenic and carcinogenic properties among a wide range of compounds. Evidence for the stimulation of synthetic processes in the cell includes the stimulation of DNA and RNA synthesis as well as protein and phospholipid synthesis. The effects of enzymatic functions in the cell are based on an increase in proteinase activity, on stimulation of ornithine decarboxylase activity, on changes in cyclic nucleotide levels, and on a decrease in histidase activity. (378 Refs)

94. NEOANTIGEN EXPRESSION IN CHEMICAL CARCINOGENESIS.

Baldwin RW, Price M

Cancer Res. Campaign Laboratories, Univ. Nottingham, Nottingham, England

Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Neoantigens have been found on tumors which were chemically induced by polycyclic hydrocarbons, by aminoazo dyes, by aromatic amines, by alkylnitrosamines, and by hydrazines. Several findings are consistent with the view that tumor-associated antigens on chemically induced tumors are expressed on integral membrane proteins or glycoproteins. Attempts to develop cell-free radioimmunoassays for these antigens have generally been unsuccessful. One of the major problems has been to retain the capacity of the radiolabeled antigens to rebind with antibodies in syngeneic immune sera. The significance of the possible relationships between tumor-associated neoantigens and products of major histocompatibility complex needs to be further evaluated. Oncodevelopmental antigens appear to be associated with numerous types of chemically induced tumors, and thus they should be regarded as valuable potential markers for studying transformation-related events. Three possible pathways leading to neoantigen expression include their appearance as a consequence of early interactions of carcinogen with target cells, their expression which only occurs once the initiated cell is converted to the preneoplastic cell, and their expression at the stage when malignant cell clones develop. (328 Refs)

95. IMPROVED TRANSFORMATION OF C3H10T1/2CL8 CELLS BY DIRECT- AND INDIRECT-ACTING CARCINOGENS.

Nesnow S, Garland H, Curtis G

Genetic Toxicology Div., Health Effects Res. Lab., United States Environmental Protection Agency, Research Triangle Park, NC, 27711

Carcinogenesis; 3(4):377-380 1982

Oncogenic transformation of C3H10T1/2CL8 cells was improved by treating the cells 5 days after seeding. Benzo[a]pyrene-induced transformation was increased 3.5-fold by this method, compared with treating the cells 1 day after seeding. N-Methyl-N'-nitro-N-nitrosoguanidine, which does not transform asynchronous cultures of C3H10T1/2CL8 cells when administered 1 day after seeding, produced an average of one focus/dish, with 61% of the dishes exhibiting foci, when administered 5 days after seeding. Propane sultone and aflatoxin B1 also produced marked transformation responses when administered 5 days after seeding. However, 4-dimethylaminoazobenzene did not induce transformation when administered either 1 day or 5 days after seeding. With all chemicals examined, clonal cytotoxicity was reduced when they were administered 5 days after seeding. These results indicate the utility of this new procedure for the qualitative analysis of the transforming ability of chemicals. (Author abstract) (28 Refs)

96. ROLE OF DNA REPAIR IN ETHYL METHANESULFONATE-INDUCED MUTAGENESIS IN SACCHAROMYCES CEREVISIAE.

Prakash L, Higgins D

Dept.Radiation Biology and Biophysics, Univ. Rochester Sch. Medicine, Rochester, NY, 14642

Carcinogenesis; 3(4):439-444 1982

Ethyl methanesulfonate (EMS)-induced reversion of two sites which revert preferentially by GC to AT transitions, cycl-131 and cycl-115, has been examined in radiation sensitive, rad, mutants of yeast belonging to the rad52 epistasis group. The rad50, rad51, rad52, rad54 and rad56 mutants showed reduced reversion of both tester sites when stationary phase diploid cells were treated with EMS. No correlation was found between EMS-induced reversion and EMS-induced homologous mitotic intragenic recombination. Survival of rad6 rad52 double mutants following EMS treatment indicates that there is one epistasis group for the repair of EMS-induced lethal damage in yeast. A model involving misrepair mutagenesis of specific lesions is proposed to account for the experimental results. (Author abstract) (39 Refs)

97. PROTECTION AGAINST FORMALDEHYDE TOXICITY BY L-ASCORBIC ACID IN RATS (MEETING ABSTRACT)

Sprince H, Smith GG, Rinehimer DA
Departments of Psychiatry and Pharmacology, Jefferson Medical College, Philadelphia, PA, 19107
148th National Meeting of the American Association for the Advancement of Science, January 3-8, 1982, Washington, D.C. American Association for the Advancement of Science 182 pp., 1982.

Formaldehyde (FMA) is an important toxicant of cigarette smoke and currently the center of controversy as a potential human carcinogen. Previously, we reported partial protection in rats (55% survivors) by single oral doses of L-ascorbic acid (LAA) against lethal (LD 95) doses of FMA. We now report additional findings pointing to LAA as a protectant against FMA. In acute toxicity tests with male rats (ca 103 days old, wt 420 gm), LAA in saline and saline controls were orally intubated 3 times within 24 hours (at 23.5, 5, 0.5 hrs) prior to oral intubation of an LD 95 dose of FMA in saline (11.0 mmoles/kg). Protection measured as percent survivors (% S) after 72 hours was: 87% S for LAA at 3 mmoles/kg vs 7% S for saline controls. LAA protection was dose-related. In chronic toxicity tests with male rats (ca 102 days old, wt 420 gm), LAA and saline controls were orally intubated 1 hour prior to an oral LD 25 dose of FMA (5 mmoles/kg) daily 5 day/week for 4 weeks. After 4 weeks, % S and mean body weights of survivors were respectively: 90% S and 416 gm for LAA at 3 mmoles/kg vs 40% S and 352 gm for saline controls and 100% S and 452 gm for untreated controls. (1 Ref)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. MICROWAVE HEATING ENHANCES THE MIGRATION OF PLASTICIZERS OUT OF PLASTICS.
Bishop CS, Dye A
East Tennessee State Univ., Johnson City, TN, 37614
J Environ Health; 44(5):231-235 1982

2. DISEASES CAUSED BY EPOXY RESINS.
Konietzko H, Fischer G
Institut fur Arbeits- und Sozialmedizin, Johannes-Gutenberg-Universitat, Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany
Zentralbl Arbeitsmed Arbeitsschutz Proph; 32(3):86-91 1982
In GER

3. NITROSAMINES.
Aigner K
Pneumonologische Abteilung, Krankenhaus der Elisabethinen, Fadingerstr. 1, A-4020 Linz-Donau, Austria
Wien Med Wochenschr; 132(71,Suppl):75-79 1982
In GER

4. EXPERIMENTAL TUMORS OF THE PERIPHERAL NERVOUS SYSTEM.
Beniashvili DS
Cancer Res. Center, Tbilisi, USSR
Eksp Onkol; 4(2):12-19 1982
In RUS

5. MUTAGENIC, CARCINOGENIC AND TERATOGENIC EFFECTS OF STYRENE.
Sram RJ, Pohlova H, Topinkova E
Klinika hygieny a epidemiologie, Srobarova 48, 100 42 Prague 10, Czechoslovakia
Prac Lek; 34(2):68-72 1982
In CZE

6. DIETHYLSTILBESTROL: EFFECT OF IN UTERO EXPOSURE.
Burke L
Obstetrics/Gynecology Dept., Harvard Medical Sch., Boston, MA
Curr Probl Obstet Gynecol; 5(2):1-58 1981

7. IN UTERO EXPOSURE TO DIETHYLSTILBESTROL: ADVERSE EFFECTS ON THE REPRODUCTIVE TRACT AND REPRODUCTIVE PERFORMANCE IN MALE AND FEMALE OFFSPRING.
Stillman RJ
Dept. Obstetrics and Gynecology, George Washington Univ. Sch. Medicine and Health Sciences, 2150 Pennsylvania Ave., NW, Washington, DC, 20037
Am J Obstet Gynecol; 142(7):905-921 1982

8. BIOLOGICAL EFFECTS OF MINERAL WOOL.
Petersen R, Ehrhorn H, Mousing K, Sabroe S, Silberschmid M, Venstrup-Nielsen SE
Socialmedicinsk institut, Vesterbro Torv 1-3, DK-8000 Arhus C, Denmark
Ugeskr Laeger; 144(13):971-975 1982
In DAN

DIETARY FACTORS IN CARCINOGENESIS

9. NATURALLY OCCURRING FOOD TOXICANTS: PHENOLIC SUBSTANCES OF PLANT ORIGIN COMMON IN FOODS.
Singleton VL
Dept. Viticulture and Enology, Univ. California, Davis, CA
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Vopr Onkol; 28(2):18-22 1982
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CHEMICAL CARCINOGENESIS

Miscellaneous Agents

SERIES CK13 No. 82/11

NOVEMBER, 1982

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HYDRAZINES AND RELATED COMPOUNDS

1. CHEMICAL AND MOLECULAR BIOLOGICAL ASPECTS ALKYLHYDRAZINE-INDUCED CARCINOGENESIS IN HUMAN CELLS IN VITRO. INTERIM REPORT, 1 SEP. 1980-31 AUG. 1981.

Witiak DT
Coll. Pharmacy, Ohio State Univ., Columbus, OH
Chemical and Molecular Biological Aspects Alkylhydrazine-induced Carcinogenesis in Human Cells In Vitro. Interim Report, 1 Sep. 1980 - 31 Aug. 1981. Available from National Technical Information Service, Springfield, VA, as N82-19833:, 20 pp., 1981.

Carbon-14 labeled 1,1-DMH and 1,2-DMH of high specific activity were prepared and utilized, along with 14C-labeled MMH, to study alkylation of DNA and proteins in low passage human neonatal foreskin derived fibroblasts. When human fibroblasts were treated under conditions which would be expected to lead to a negligible number of transformation events, ie cells labeled were in a non-growing environment and the dose of methylhydrazine (1.6 microgram/ml) was well below the ED50 value (62-100 microgram/ml), significant differences in DNA and protein methylation were observed. For both protein and DNA, 1,2-DMH produced a higher degree of methy-

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lation than 1,1-DMH, with MMH demonstrating the lowest level. The data suggests that in these cells there are significant differences in the metabolic and/or chemical transformation of the methylhydrazines in the proposed active metabolite, methyl diazonium ion. (Author abstract)

2. CELL SPECIFICITY IN HEPATOCARCINOGENESIS: PREFERENTIAL ACCUMULATION OF O(6)-METHYLGUANINE IN TARGET CELL DNA DURING CONTINUOUS EXPOSURE OF RATS TO 1,2-DIMETHYLHYDRAZINE.

Bedell MA, Lewis JG, Billings K C, Swenberg JA
Dept. Pathology, Chemical Industry Inst. Toxicology, Research Triangle Park, NC, 27709
Cancer Res; 42(8):3079-3083 1982

Concentrations of the major methylated DNA purines were determined in two liver cell populations of Fischer 344 rats during administration of 30 ppm 1,2-dimethylhydrazine (SDMH) in the drinking water for periods of up to 4 wk. Quantitation of 7-methylguanine and O6-methylguanine (O6MG) was achieved by highly sensitive optical methods following separation of DNA bases by high-performance liquid chromatography. Overall alkylation as indicated by the concentration of 7-methylguanine was near max in both hepatocytes and liver nonparenchymal cells by the third day of SDMH administration. Similar amounts of 7-methylguanine were present in the two liver cell populations at seven of nine time points during 4 wk of exposure. In contrast, dramatic differences in the cumulative concentrations of O6MG were seen in the two cell populations. Nonparenchymal cells accumulated O6MG during the first 8 days of exposure and had up to a 30-fold greater concentration of this product than did the corresponding hepatocytes. In the hepatocytes, a rapid decline in O6MG concentration was observed between 1 and 3 days of exposure to SDMH. Thereafter, only low levels of this promutagenic lesion were present in hepatocytes. Exposure of rats to the same regimen of SDMH for up to 10 mo caused angiosarcomas in the livers of over 90% of the animals, while hepatocellular carcinomas occurred in only 40%. Thus, a strong correlation exists between the inability to repair O6MG and cell specificity for carcinogenesis. (Author abstract) (50 Refs)

HETEROCYCLIC COMPOUNDS

3. CHROMOSOMAL ABERRATIONS INDUCED BY ETHYLENE OXIDE IN A HUMAN AMNIOTIC CELL LINE IN VITRO.

Poirier V, Papadopoulo D
Section de Biologie, Institut Curie, 26 rue d'Ulm, 75231 Paris Cedex 05, France
Mutat Res; 104(4/5):255-260 1982

Effects of ethylene oxide (EO) on the induction of chromosomal aberrations were studied in the human FL cell line and the results are discussed. The range of EO doses, 5, 7, and 10 milliM (mM)/hr, which led to cell survival of 58, 25, and 9.2% were used. Cells kept in phosphate-buffered saline for the same length of time served as controls. The majority of induced aberrations were of the chromatide type such as: gaps, breaks, exchanges, and 'complexes'. Several metaphases with aberrations were observed in the control cultures at each fixation time. Significant increase as a function of EO doses was observed in the frequencies of chromosomal aberrations of all categories. The number of aberrant metaphases in the cultures treated at 5, 7, and 10 mM/hr was 21.3, 65.6, and 74.9%, respectively, at 48-hr fixation time. The number of aberrations/metaphase increased in treated cultures, 2x for 5 mM/hr, 10x for 7.5 mM/hr, and 36x for 10 mM/hr EO. The number of observed breaks increased 4-, 10-, and 50-fold with increasing concentration of EO. The number of chromatid exchanges increased for approx 2-, 10-, and 20-fold in EO-treated cultures. Multiple aberrations scored as 'complexes' appeared only in 7.5 mM/hr-treated cells and their number increased 10-fold in 10 mM/hr-treated cells. The frequencies of induced aberrations varied with the post-treatment time. Except for the gaps, the observed frequencies of chromosomal aberrations decreased slowly and gradually until 96 hr after treatment. A dose of 12.5 mM/hr appeared to be toxic (4% survival level) for the production of good metaphase chromosome preparations. (24 Refs)

4. COMPARISON OF CELLULAR GROWTH CHARACTERISTICS OF TRANSFORMED C3H 10T-1/2 CELLS ISOLATED FROM 14 DAY COLONY AND 38 DAY FOCUS AFTER EXPOSURE TO BENZO(A)PYRENE AND 1,3-DL-DIEPOXYBUTANE (MEETING ABSTRACT).

Nelson RL, Garry VF
University of Minnesota, Minneapolis, MN, 55455
In Vitro; 18(3,part2):299 1982

Utilization of the C3H 10T-1/2 clonal cell line for morphologic transformation by chemical carcinogens has been restricted by the necessity of prolonged cultivation (4-6 weeks) before morphologic transformants can be accurately identified. In this report, we will present evidence for the observation of morphologic transformation of C3H 10T-1/2 colonies in 14 to 16 days after 24 hour carcinogen exposure to dose increments of Benzo(a)pyrene and diepoxybutane. Morphologic scoring of transformants is similar to the criteria put forward by Reznikoff et al. Overall, colony transformation frequencies appear to be lower than focus transformation frequencies by a factor of 2 at the corresponding dose. Transformed colony and foci isolates were compared for the following growth parameters at 2, 5, and 10 passages: plating efficiency, soft agar growth, doubling time and saturation density. Serial subcultivation of transformants shows marked differences in soft agar growth and saturation density patterns. Characteristically, foci isolates show rapid adaptation to soft agar growth; whereas transformed colony isolates are slowly adapted. Similar differences in the saturation density patterns of the isolates were noted. (no Refs)

INORGANIC AGENTS AND PARTICULATES INCLUDING FIBERS

5. INDUCTION OF OCULAR NEOPLASMS IN FISCHER RATS BY INTRAOCULAR INJECTION OF NICKEL SUBSULFIDE.

Albert DM, Gonder JR, Papale J, Craft JL, Dohlman HG, Reid MC, Sunderman FW
Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA, 02114
Invest Ophthalmol Vis Sci; 22(6):768-782 1982

Carcinogenesis bioassay results of administration of a single intraocular injection of 0.5 mg nickel bisulfide (NBS) into Fisher rats are reported. Minimal inflammation was observed at the injection sites in the first wk after administration. An ocular tumor was first observed at 26 wk. This tumor grew rapidly and eventually replaced the entire orbit. When the rat was killed at 30 wk after injection, the tumor had invaded the cranium by extension along the optic nerve to the optic chiasm and had metastasized to the cerebrum and lung. Between wk 34-36, ocular neoplasms became clearly visible in 13/14 treated rats. By 40-42 wk, malignant ocular tumors were observed in 14/15 injected eyes of treated rats vs 0/11 injected eyes of control rats. Five of the treated eyes contained multiple neoplasms. The 21 distinct ocular tumors that were identified by histologic examination included 11 melanomas, four retinoblastomas, three gliomas, and three unclassified malignant neoplasms. The presence of melanosomes in some of the ocular melanomas arising from amelanotic uveal melanocytes was unusual. Short latency period, high tumor yield, and ease of tumor detection make this an attractive experimental model for research on metal carcinogenesis. (29 Refs)

6. VIDEO TIME-LAPSE MICROSCOPY OF PHAGOCYTOSIS AND INTRACELLULAR FATE OF CRYSTALLINE NICKEL SULFIDE PARTICLES IN CULTURED MAMMALIAN CELLS.

Evans RM, Davies PJ, Costa M
Dept. Pharmacology, Univ. Texas Medical Sch. at Houston, Houston, TX, 77025
Cancer Res; 42(7):2729-2735 1982

The endocytosis and intracellular distribution of carcinogenic crystalline nickel sulfide (NiS) particles in Chinese hamster ovary cells were studied using time-lapse video recording with phase-contrast and bright-field optics. Crystalline NiS particles were phagocytosed by Chinese hamster ovary cells in regions of membrane ruffling. While these particles may remain bound to the cell surface for variable time intervals (min to hr), their internalization generally required only 7 to 10 min. Endocytosed crystalline NiS particles exhibited saltatory motion, and lysosomes were observed to interact repeatedly with the particles in a manner similar to that observed during the digestion of macropinosomes. Particles were never observed to be exocytosed from the cell, and with time, most of the internalized particles aggregated in the region around the nucleus. After 24 to 48 hr, particle saltation decreased to a point where the particle position became relatively fixed in the perinuclear region, and in some instances, this was associated with a conspicuous vacuole formation around the particles. It is concluded that the uptake and distribution of crystalline NiS particles occur by normal endocytic and saltatory processes as occur during the formation and breakdown of macropinosomes. The observed lysosomal interaction with phagocytosed cytoplasmic NiS may accelerate particular nickel dissolution allowing entry of ionic nickel into the nucleus. (Author abstract) (30 Refs)

7. CHROMIUM AS A PROBLEM IN PHYSIOLOGY, EPIDEMIOLOGY, AND IN BIOLOGICAL MONITORING.

Hertel RF
Munster-Roxel, W. Germany
Staub Reinhalt Luft; 42(4):135-137 1982

The physiological effects of chromium depend on the oxidation state. Chromium III is thought to have a protective effect on the cardiovascular system. Carcinogenesis has been attributed to chromium VI. Chromium VI may serve only as a vehicle, requiring reduction to chromium III, since chromium VI apparently does not cross cell membranes or bind DNA. The principle test for occupational exposure to chromium is a urine test. Sputum, blood, and bilirubin may also be analyzed. (38 Refs) (In GER)

8. EVALUATION OF THE MUTAGENIC POTENTIAL OF THE ENVIRONMENTAL POLLUTANT MERCURIC CHLORIDE.

Vasil'eva IM, Sdirkova NI, Zasukhina GD, Butenko PG, Krasovskii GN, Vasiukovich LIa

Inst. General Genetics, Moscow, USSR

Tsitol Genet; 16(2):21-24 1982

Potential mutagenicity of mercuric chloride (MC) was studied in vitro and in vivo. MC produced a dose-dependent increase in the incidence of single-stranded DNA breaks in cultured rat embryonal fibroblasts (REF). Treatment of pox virus vaccine with MC reduced its viability in the REF. Analysis of the offspring of male albino rats that were subjected to chronic exposure to MC at 0.00025 or 0.0025 mg/kg showed an increase in embryo lethality and decreases in the number and wt of the embryos. (4 Refs) (In RUS)

9. SURVEY OF TOXICITY AND CARCINOGENICITY OF MINERAL DEPOSITS.

Furst A, Harding-Barlow I

Lawrence Livermore Natl. Lab., Livermore, CA

Survey of Toxicity and Carcinogenicity of Mineral Deposits. Available from National Technical Information Service, Springfield, VA, as DE82003164:, 101 pp., 1981.

The toxicities and biogeochemical cycles of arsenic, cadmium, chromium, lead and nickel are reviewed in some detail, and other trace elements briefly mentioned. These heavy metals are used as a framework within which the problem of low-level radioactive waste disposal can be compared. (Author abstract)

10. THE HEALTH EFFECTS OF COAL-BURNING POWER PLANTS IN MINNESOTA.

Ross D

Minnesota Public Interest Res. Foundation, Minneapolis, MN

The Health Effects of Coal-Burning Power Plants in Minnesota. Available from National Technical Information Service, Springfield, VA, as PB82-158544:, 54 pp., 1981.

The carcinogenic properties of coal combustion products are described and documented with emphasis on beryllium, mercury, and other particulates. Increased coal use in Minnesota and implications of such increases for 1976-1995 are discussed. Details of how a coal-fired power plant works and how pollutants are formed are described. Efforts to minimize health impacts of sulfur oxides and particulates are detailed. An analysis is provided of how health impacts are measured, showing how a lack of precision and data makes it difficult for policymakers to decide which pollutants need regulation and how much regulation is required. It was found that the greatest problem resulting from coal burning in Minnesota is fine particulate pollution. Fine particulates have been implicated in the exacerbation of emphysema, bronchitis, and lung cancer. Increased regulation and limitations on the construction of coal burning electricity generators are supported. (Author abstract)

11. ASBESTOS CARCINOGENESIS: ASBESTOS INTERACTIONS AND EPITHELIAL LESIONS IN CULTURED HUMAN TRACHEOBRONCHIAL TISSUES AND CELLS.

Haugen A, Harris C
Div. Cancer Cause and Prevention, NCI, Bethesda, MD
Recent Results Cancer Res; 82:32-42 1982

Experimental studies relevant to the evaluation of carcinogenic risk of asbestos in the respiratory tract are reviewed. That asbestos fibers are carcinogenic has been established beyond question. Chrysotile can act as a cocarcinogen in 7,12-dimethylbenz(a)anthracene exposed rat tracheal transplants, and has also been shown to be weakly carcinogenic in tracheal transplants. Asbestos may derive its carcinogenicity from either the presence of carcinogens which contaminate its surface, or from the physical structure of the asbestos fibers themselves. Recent research supports the latter concept, especially when one considers that the induction of mesotheliomas by asbestos is strictly dependent upon the size of the inducing particles. Furthermore, benzene-extracted crocidolite induces the same number of tumors as does non-extracted crocidolite. Asbestos fibers contain metals including iron, magnesium, and aluminum as major constituents, and nickel, chromium, cobalt, and others as trace elements. Nickel and chromium are considered to be respiratory carcinogens. Asbestos fibers may, because of their absorptive properties, act in conjunction with metals and chemical carcinogens. In vitro studies using cultured tissues and cells are described. (53 Refs)

AMIDES, CARBAMATES AND UREAS

12. LABELED 1,N(6)-ETHENOADENOSINE AND 3,N(4)-ETHENOCYTIDINE IN HEPATIC RNA OF MICE GIVEN [ETHYL-1,2-3H OR ETHYL-1-14C] ETHYL CARBAMATE (URETHAN).

Ribovich ML, Miller JA, Miller EC, Timmins LG
(c/o Miller) McArdle Lab. Cancer Res., Univ. Wisconsin Center Health Sciences, 450 North Randall Ave., Madison, WI, 53706
Carcinogenesis; 3(5):539-546 1982

Injection of a single dose of [ethyl-1,2-3H] or [ethyl-1-14C]ethyl carbamate into 12-day old male [C57BL/6 x C3H/He]F1 mice or of [ethyl-1,2-3H]ethyl carbamate into adult male A/Jax mice resulted in the formation of labeled 1,N6-ethenoadenosine and 3,N4-ethenocytidine adducts in the hepatic RNA. These adducts were characterized by comigration on hplc of 3H or 14C in enzymatic hydrolysates of the RNA with synthetic standards. Both the ethenoadenosine and ethenocytidine were further characterized by their conversion to acetylated products that comigrated with acetylated synthetic standards. The ethenoadenosine was also converted by anhydrous trifluoroacetic acid to a product that comigrated with synthetic 1,N6-ethenoadenine. The levels of adducts in the hepatic RNA 12 hr after a single injection of 0.5-0.6 mg of ethyl carbamate/g body wt were 6-10 and 2-3 pmol/mg RNA of ethenoadenosine or ethenocytidine, respectively. No labeled ethenoadenosine or ethenocytidine could be detected in the hepatic RNA of mice given [1-14C]ethanol, an enzymatic hydrolysis product of ethyl carbamate. These data indicate that ethyl carbamate may be metabolically activated by dehydrogenation to vinyl carbamate and subsequent epoxidation of the latter compound as previously proposed. Vinyl carbamate epoxide may form etheno derivatives in a manner analogous to that demonstrated for chloroethylene oxide, an electrophilic metabolite of vinyl chloride. Vinyl carbamate has been shown to have the same spectrum of tumor induction as ethyl carbamate but to be much more active than the latter carcinogen. (Author abstract) (37 Refs)

13. SEQUENTIAL 2-ACETYLAMINOFLUORENE-PHENOBARBITAL EXPOSURE INDUCES A CYTOSOLIC ALDEHYDE DEHYDROGENASE DURING RAT HEPATOCARCINOGENESIS.

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Carcinogenesis; 3(5):533-538 1982

A significant change in hepatic aldehyde dehydrogenase activity has been observed in normal Sprague-Dawley rat liver during the promotion phase of hepatocarcinogenesis induced by brief feeding of 2-acetylaminofluorene (2-AAF) followed by tumor promotion using dietary phenobarbital (PB) exposure. Animals receiving only 2-AAF or PB do not possess this new aldehyde dehydrogenase activity. The phenotype is characterized by the appearance of a new cytosolic isozyme kinetically, electrophoretically and immunochemically distinct from the normal liver aldehyde dehydrogenase isozymes and from aldehyde dehydrogenases inducible in 2-AAF-induced hepatomas. The new isozyme is NAD-dependent, disulfiram-sensitive and cross-reacts with antiserum to a normal liver aldehyde dehydrogenase inducible in several lines of rats by PB. However, the population of animals used in this study has been shown previously to be non-responsive to aldehyde dehydrogenase induction by dietary PB. Since no animals receiving only PB express this new isozyme, the carcinogen must play a significant role in its induction. Moreover, that not all animals receiving carcinogen and promoter possess the phenotype suggests this carcinogen/promoter interaction has a genetic basis. (Author abstract) (19 Refs)

14. FORMATION OF 6-DIMETHYLCARBAMYLOXY-DGUO, 6-DIMETHYLAMINO-DGUO AND 4-DIMETHYLAMINO-DTHD FOLLOWING IN VITRO REACTION OF DIMETHYLCARBAMYL CHLORIDE WITH CALF THYMUS DNA AND 6-DIETHYLCARBAMYLOXY-DGUO FOLLOWING IN VITRO REACTION OF DIETHYLCARBAMYL CHLORIDE WITH CALF THYMUS DNA.

Segal A, Solomon JJ, Mate U, Van Duuren BL
Lab. Organic Chemistry and Carcinogenesis, Inst. Environmental Medicine, New York Univ. Sch. Medicine, New York, NY, 10016
Chem Biol Interact; 40(2):209-231 1982

The rodent carcinogens dimethylcarbamyl chloride (DMCC) and diethylcarbamyl chloride (DECC) react with dGuo (pH 7.0-7.5, 37 C, 4 hr) to form the O6-acyl derivatives 6-dimethylcarbamyloxy-2'-deoxyguanosine (6-DMC-dGuo) and 6-diethylcarbamyloxy-2'-deoxyguanosine (6-DEC-dGuo), respectively. Reaction of DMCC with dThd under identical conditions yielded 4-dimethylamino-thymidine (4-DMA-dThd). Compounds 6-DMC-dGuo and 6-DEC-dGuo undergo a nucleophilic aromatic substitution reaction with dimethylamine (DMA) to form 6-dimethylamino-2'-deoxyguanosine (6-DMA-dGuo) via displacement of the C-6 dialkylcarbamyloxy moiety. The substitution reaction did not take place when diethylamine or NH3 were substituted for DMA. The structures of the new compounds 6-DMC-dGuo, 6-DEC-dGuo, 4-DMA-dThd and 6-DMA-dGuo were deduced from chemical analyses and syntheses, UV and nuclear magnetic resonance (NMR) spectra and electron impact, isobutane chemical ionization and source insertion isobutane chemical ionization mass spectra. It was postulated that 4-DMA-dThd was formed following reaction of the transient intermediate 4-DMC-dThd with DMA formed by hydrolysis of DMCC. Calf thymus DNA was reacted in vitro with DMCC (pH 7.0-7.5, 37 C, 4 hr) and the modified DNA hydrolyzed enzymatically to 2'-deoxynucleosides. Compounds 6-DMC-dGuo, 4-DMA-dThd and 6-DMA-dGuo were identified in the hydrolysate by high-pressure liquid chromatography (HPLC). In an identical manner 6-DEC-dGuo was identified following in vitro reaction of DECC with calf thymus DNA. Compounds 6-DEC-dGuo and 6-DMC-dGuo possess novel structures with respect to the types of adducts known to be formed between carcinogens and bases in DNA. The implications of these findings with respect to chemical mutagenesis and carcinogenesis is discussed. The structural relationship between N4-dimethyl-5-methylcytosine (4-dimethylamino-Thy) formed in DNA following in vitro reaction with DMCC and 5-methylcytosine, the only modified base found in vertebrate DNA is noted. (Author abstract) (47 Refs)

AMINO ACID ANALOGS AND MODIFIED NUCLEIC ACID CONSTITUENTS

15. 5-BROMODEOXYURIDINE INDUCED SISTER CHROMATID EXCHANGE FREQUENCIES IN PRIMATE LYMPHOCYTES.

Barnett RI, Wallace JA
Dept. Anatomy, Queen's Univ., Kingston, Ontario K7L 3N6, Canada
Experientia; 38(5):542-543 1982

Comparisons of SCE frequencies at various BrdUrd concentrations showed significant interspecies differences with human lymphocytes being the most sensitive. (Author abstract) (16 Refs)

16. BINDING OF [14C]-AZASERINE TO DNA AND PROTEIN IN THE RAT AND HAMSTER.

Zurlo J, Coon CI, Longnecker DS, Curphey TJ
New York Univ. Medical Center, Inst. Environmental Medicine, 550 First Ave., New York, NY, 10016
Cancer Lett; 16(1):65-70 1982

Binding and subsequent removal of radioactivity in DNA and protein of various target and nontarget organs after administration of 14C-azaserine were compared in Lewis rats and Syrian golden hamsters. Rats develop acinar cell abnormalities and pancreatic tumors in response to AS treatment, while hamsters do not. In rats, after 90 min the greatest amount of binding to DNA occurred in the liver, while binding to DNA of pancreas and kidney occurred to a leser extent. After 24 hr, 55% of the DNA-associated radioactivity had been removed from liver, 16% from kidney and 49% from pancreas, bringing the specific activity of DNA in these three organs to nearly the same level. Protein from liver also exhibited higher specific activity than did that from the other organs 90 min after AS treatment. While the levels of radioactivity in kidney and thymus were comparable in rat and hamsters, the specific activities of DNA and protein from hamster pancreas were each about 2x those from rat pancreas. Hamster liver DNA was also more extensively labeled than both rat liver DNA and hamster pancreatic DNA. These results indicate that binding of 14C-AS to DNA and protein do not correlate with species or tissue susceptibility to carcinogenesis by AS. (15 Refs)

17. POTENT ANTIVIRAL 2'-FLUORO-ARABINOSYL PYRIMIDINE NUCLEOSIDES: LACK OF MUTAGENIC ACTIVITY.

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Carcinogenesis; 3(5):593-596 1982

The carcinogenicity of many drugs, such as antitumor agents, is a subject of growing concern. The newly developed pyrimidine nucleosides, 2'-fluoro-5-iodo-1-beta-D-arabinofuranosylcytosine (FIAC) and 2'-fluoro-1-beta-D-arabinofuranosyl-5-methyluracil (FMAU), have shown potent antiherpes virus activity in tissue cultures, laboratory animals and man and an activity to inhibit the growth of certain tumor cell lines in vitro. Radioactivity of 14C-labeled FIAC and FMAU is incorporated into the DNA of normal and neoplastic mammalian tissues. However, we now report that FIAC and FMAU are inactive in a bacterial mutagenesis assay (Salmonella-microsome test) and in a mammalian cell mutagenesis assay employing V79 Chinese hamster cells in vitro. Both agents did not induce unscheduled DNA synthesis in primary Wistar rat hepatocytes in vitro. (Author abstract) (7 Refs)

ALIPHATIC HALOGEN COMPOUNDS

18. CHANGES OF HEPATOCYTE PROLIFERATION IN MOUSE LIVER AND ADENOMATOUS NODULES DURING CCL4-INDUCED CARCINOGENESIS.

Faktor VM, Poltoranina VS, Uryvaeva IV
Lab. Cytology, N. K. Kol'tsov Inst. Biology Development, Moscow, USSR
Biull Eksp Biol Med; 93(4):79-82 1982

The effect of CCl4-induced carcinogenesis on hepatocyte proliferation was studied in SWR mice. Development of liver necrosis and foci of nodular proliferation was associated with marked decrease of the ploidy and the increase of the incidence of chromosome aberrations. These findings indicate that the early stages of liver carcinogenesis are characterized by the impairment of the mechanism of mitotic polyploidization. (13 Refs) (In RUS)

19. EFFECT OF CARBON TETRACHLORIDE ON THE INDUCTION AND DEVELOPMENT OF HEPATOMA INDUCED BY 2-N-ACETYLAMINOFLUORENE IN INBRED WISTAR RATS.

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Patol Pol; 32(4):471-486 1981

The effect of carbon tetrachloride (CT) on histological changes induced by 2-N-acetylaminofluorene (AAF) in the livers of 3-mo-old inbred male and female Wistar rats was studied. The substances were administered simultaneously through gastric probes for 3-5 mo at which time some of the animals were decapitated. The hepatic lesions were found to be more pronounced in the group treated with CT only (0.2 ml/day) than in those treated with AAF only (15 mg/day). Focal nodular hyperplasia was found in both groups at mo 5 but not at mo 3. Benign or malignant multifocal hepatomas were found in all animals decapitated after 5-mo treatment with both CT (2 ml) and AAF (15 ml), but only multifocal benign hepatomas or focal nodular hyperplasia were found in the animals decapitated after 3 mo of treatment. Multifocal benign hepatomas and focal nodular hyperplasia were found in another group treated with reduced doses of CT (0.1 ml/day) and AAF (7.5 mg/day) for 3 mo, and all animals treated with such doses for 5 mo developed multifocal benign hepatomas. The findings indicated that the hepatic changes observed were a combination of the lesions induced by the two substances. (28 Refs) (In POL)

20. VINYL CHLORIDE-INDUCED HEPATIC LESIONS IN MAN AND RODENTS. A COMPARISON.

Popper H, Maltoni C, Selikoff IJ
Stratton Lab. for the Study of Liver Disease, Mount Sinai Sch. Medicine, City Univ. New York, New York, NY
Liver; 1(1):7-20 1981

Parallel sequences in the liver of man, rats, and mice exposed to vinyl chloride (VC) were compared to review pathologic features induced, to document similarities in evolution from precursor lesions to malignant states, and to compare the evolution with that caused by other carcinogenic agents. Available for study were 19 human cases of angiosarcoma and precursor lesions following exposure to VC, previously reported, plus 5 additional angiosarcomas (autopsy) and 16 precursor lesions (biopsy material). Rats and mice had been exposed to VC in inhalation chambers. In man, the number of sinusoidal cells conspicuously increased and they almost filled the spaces between the enlarged hepatocytes. In rodents, the variety of sinusoidal cells was less conspicuous and fewer macrophages were found, but lining cells with large polychromatic nuclei similarly predominated. In man and rodents, progression of the sinusoidal dilatation associated with proliferation of the hepatocytes and sinusoidal cells loosened the parenchymal architecture. Nodules consisting of angiosarcoma cells were noted in man and rodents. Most consisted of spindle-shaped cells, in part in vascular spaces which, however, in part were also lined by nontumorous endothelial cells. In addition, in man, nodules consisted of large polyhedral sarcoma cells with abundant eosinophilic cytoplasm. The center of these nodules usually exhibited hemorrhagic necrosis and these cells then lined bloody cysts. The demonstrated similarity of the evolution in man and rodent strongly supports the extrapolation of observations from experimental animals to man. (58 Refs)

21. CHLOROFORM: A REVIEW OF ITS METABOLISM, TERATOGENIC, MUTAGENIC, AND CARCINOGENIC POTENTIAL.

Davidson IW, Sumner DD, Parker JC
(c/o Parker) ECAO, Environmental Protection Agency, MD-52, Research Triangle Park, MD, 27711
Drug Chem Toxicol; 5(1):1-87 1982

The toxicology of chloroform is reviewed in detail. Included are discussions of the following: absorption routes (oral and pulmonary); tissue distribution; excretion (pulmonary and other routes, bioaccumulation); biotransformation (known metabolites, magnitude of chloroform metabolism, enzymatic pathways of biotransformation); covalent binding (proteins and lipids, including differences due to genetic strains, sex, interspecies, and age; binding to nucleic acids; role of phosgene; role of glutathione); mutagenicity in vitro and in vivo; carcinogenicity (animal and epidemiological studies); teratogenicity; and risk considerations (one-hit and multi-hit models). The potential of adverse health effects from exposure to chloroform in the environment is of increasing concern. (162 Refs)

22. DOMINANT LETHAL STUDY IN RATS WITH 1,2-DIBROMO-3-CHLOROPROPANE AND ITS STRUCTURALLY RELATED COMPOUNDS.

Saito-Suzuki R, Teramoto S, Shirasu Y
Toxicology Div., Inst. Environmental Toxicology, Suzuki-cho, 2-772, Kodaira-shi, Tokyo 187, Japan
Mutat Res; 101(4):321-327 1982

A dominant lethal experiment was conducted in male SD rats using 1,2,3-tribromopropane (TBP), 1,2-dibromopropane, 1-bromopropane, 1,2,3-trichloropropane, and 1-chloropropane, all structurally related to 1,2-dibromo-3-chloropropane. Throughout the experiment, no difference in mating performance was noted between control and test groups. The percentage impregnation for the TBP-treated group was significantly decreased (33-73%) at wk 3 and 5-8. The other compounds did not reduce the frequency of fertile matings. (18 Refs)

POLYHALOGENATED RING COMPOUNDS INCLUDING INSECTICIDES

23. TOXICITY OF POLYBROMINATED BIPHENYLS (PBBS) IN DOMESTIC AND LABORATORY ANIMALS.

Damstra T, Jurgelski W, Posner HS, Vouk VB, Bernheim NJ, Guthrie J, Luster M, Falk HL
Natl. Inst. Environmental Health Sciences, Post Office Box 12233, Research Triangle Park, NC, 22709
Environ Health Perspect; 44():175-188 1982

Chemical composition and fate of polybrominated biphenyls (PBBs) in the environment, absorption, distribution, biotransformation, and elimination of PBBs, enzyme induction by PBBs, chemical interaction of PBBs with other chemicals and drugs, general toxicity, neurobehavioral toxicity, immunotoxicity, reproductive toxicity, mutagenicity, and carcinogenicity of PBBs involved in accidental contamination of cattle feed in Michigan in 1973 are reviewed. Mutagenicity studies on PBBs to date have been negative but inadequate. Exposure to high doses of PBBs have been shown to cause liver cancer in rats and mice. (117 Refs)

24. TETRACHLORODIBENZODIOXIN: A SURVEY OF SUBJECTS TEN YEARS AFTER EXPOSURE.

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Br J Ind Med; 39(2):128-135 1982

Ten years after an incident following which 79 workers developed chloracne due to exposure to tetrachlorodibenzodioxin a study was undertaken to establish the current state of health of the affected employees remaining in the company's (Coalite Oils and Chemicals Ltd, a subsidiary company of Coalite Group Ltd) employment. The opportunity was used to examine effects on mortality, morbidity, carcinogenesis, reproduction, teratogenicity, fetotoxicity, biochemistry, immunology, and genetic change. Concurrently, control groups were established with which to make comparison. The control groups selected from within the works matched the study group in respect of sex and age but it was not possible to match them for occupation and social status. Half the affected subjects still have minor chloracne. Other than this there is no evidence that they have been adversely affected in any way. (Author abstract) (24 Refs)

25. EFFECT OF THE INSECTICIDES TOXAPHENE AND CARBARYL ON INDUCTION OF LUNG TUMORS BY BENZO(A)PYRENE IN THE MOUSE.

Triolo AJ, Lang WR, Coon JM, Lindstrom D, Herr DL
Dept. Pharmacology, Jefferson Medical Coll., 1020 Locust St., Philadelphia, PA, 19107
J Toxicol Environ Health; 9(4):637-649 1982

The modulating effects of toxaphene (TOX) and carbaryl (CAR) upon benzo(a)pyrene (BP)-induced lung tumors and on BP hydroxylase activity in liver and lung were investigated. Female A/J mice were fed TOX (100 or 200 ppm) or CAR (1,000 ppm) in the diet, and administered 3 mg BP po on day 7 and day 21. No control animals or animals fed TOX alone but all BP induced and BP-induced plus TOX animals developed forestomach tumors at 12 wk. These tumors were well-developed squamous cell papillomas. While TOX alone produced no effect upon spontaneous lung tumors, feeding 100 ppm TOX to BP-induced animals caused a slight but statistically significant decrease in the incidence of lung tumors. The higher dose TOX, however, had no effect. Both TOX doses increased BP hydroxylase activity in liver but decreased it in lung. Combined TOX plus BP followed a similar pattern. Although feeding 200 ppm TOX for 20 wk alone did not affect lung tumor incidence in BP-treated mice, it markedly decreased the mean number of tumors per mouse and the percent of BP-induced lung tumors. Feeding 1,000 ppm CAR caused a modest increase in the incidence of BP-induced lung tumors. In a second experiment, however, no significant differences in lung tumor incidence were observed between controls and CAR-fed mice. Feeding CAR with BP did not affect liver BP hydroxylase activity but did significantly increase the activity of this enzyme in the lung. (47 Refs)

DRUGS, COSMETICS, DETERGENTS AND OTHER COMMERCIAL MATERIALS

26. MORPHOLOGICAL AND NEOPLASTIC TRANSFORMATION OF SYRIAN HAMSTER EMBRYO FIBROBLASTS BY DIETHYLSTILBESTROL AND ITS ANALOGS.

McLachlan JA, Wong A, Degen GH, Barrett JC
Transplacental Toxicology Section, Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, NC, 27709
Cancer Res; 42(8):3040-3045 1982

A mammalian cell culture system using normal, diploid Syrian hamster embryo fibroblasts was used as a model to study the ability of diethylstilbestrol (DES) and related compounds to induce neoplastic transformation. Like benzo(a)pyrene, a known chemical carcinogen, DES (0.01 to 10 ug/ml) induces morphological transformation of Syrian hamster embryo fibroblasts in vitro; the transformed colonies were indistinguishable from colonies of benzo(a)pyrene-transformed cells. The morphologically transformed colonies derived from either benzo(a)pyrene- or DES-treated cells were tumorigenic when injected into newborn hamsters. At doses of 0.01 to 1 ug/ml for 48 hr, DES did not inhibit or stimulate cell proliferation. Structural analogous of DES were also tested in the Syrian hamster embryo transformation system. Like DES, tetrafluoro-diethylstilbestrol, dimethylstilbestrol, and cis,cis-dienestrolmorphologically transformed Syrian hamster embryo cells. The transformation frequency of dimethylstilbestrol was much less than that of DES, tetrafluorodiethylstilbestrol, or cis,cis-dienestrol. Hexestrol, dimethoxydiethylstilbestrol, and trans,trans-dienestrol did not transform these cells. No correlation could be demonstrated between reported estrogenic potency of the compounds and their cell-transforming capacity. Structure-activity relationships developed for these chemicals suggest that metabolism via specific pathways plays a role in DES-induced cell transformation. (Author abstract) (33 Refs)

27. A STUDY ON THE MUTAGENICITY OF PHENOBARBITONE USING THE MICRONUCLEUS TEST IN SWISS MICE.

Nandan SD, Rao S
Dept. Genetics, Osmania Univ., Hyderabad 500 007, India
IRCS Med Sci [Cancer]; 9(10):937-938 1981

The chromosome-breaking potential of phenobarbitone in bone marrow cells of Swiss mice was assessed employing the micronucleus test. A statistically significant and dose-dependent increase in the frequency of micronuclei was observed in the polychromatic and normochromatic erythrocytes at drug doses of 84 and 126 mg/kg body wt, while no significant increase in the micronulcei was detected with 42 mg/kg. Results indicated that phenobarbitone is capable of causing chromosome damage in the bone marrow cells of mice. (14 Refs)

28. QUANTITATIVE CHANGES IN ESTROGEN RECEPTOR PRODUCED BY CHRONIC DES TREATMENT OF TWO MOUSE STRAINS DIFFERING IN SUSCEPTIBILITY TO LEYDIG CELL TUMOR INDUCTION.

Terakawa N, Huseby RA, Fang SM, Samuels LT
Dept. Obstetrics and Gynecology, Osaka Univ. Medical Sch., 1-1-50 Fukushima, Fukushima-ku, Osaka, Japan
J Steroid Biochem; 16(5):643-652 1982

The effects of chronic diethylstilbestrol (DES) treatment on the estrogen receptor system in testes of BALB/c mice, which develop Leydig cell tumors after long-term DES, and C3H mice, which do not, were investigated. Estrogen receptor concentration in Leydig cell cytosols from C3H mice was similar to that observed in BALB/c mice at the beginning of DES treatment, but changed during long-term estrogenization. Estrogen receptor sites in cytosol increased significantly in BALB/c mice during DES treatment without any alteration in affinity for estrogen. A similar but lesser increase was observed in C3H mice. A single DES treatment caused an increase of nuclear receptor content in BALB/c mice which was greater than that observed in C3H mice. In C3H testes the nuclear estrogen receptor content remained constant after 7-14 days treatment while that in BALB/c mice rose to a level 150% that observed 0.75 hr after a single injection of 2.5 ug DES. These differences in nuclear receptors parallel differences in both early induction of DNA synthesis in Leydig cells and the induction of Leydig cell tumors observed in the two strains. (26 Refs)

29. EFFECT OF PRAZIQUANTEL, A NEW ANTISCHISTOSOMAL DRUG, ON THE MUTATION AND TRANSFORMATION OF MAMMALIAN CELLS.

Billings PC, Heidelberger C
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Cancer Res; 42(7):2692-2696 1982

Praziquantel (PQ), a tetrahydroquinoline derivative, is a new clinically effective antischistosomal drug, which has been shown to lack or to possess very weak mutagenic activity.

However, in bacteria, this compound can act as a weak comutagen that increases the mutagenicity of several chemical mutagens and carcinogens. We have found that PQ can act as a very weak comutagen in animal cells. At 10 to 50 ug/ml, PQ increased the mutagenicity of N-methyl-N'-nitro-N-nitrosoguanidine and 2-methoxy-6-chloro-9-[3-(2 chloroethyl)aminopropylamino]acridine dihydrochloride about two-fold in Chinese hamster V-79 cells. In C3H/10T1/2 mouse embryo cells, PQ exhibited only negligible comutagenic activity. PQ did not oncogenically transform C3H/10T1/2 cells but had a pronounced effect on 3-methylcholanthrene-induced transformation of these cells. When PQ was coadministered with or added after 3-methylcholanthrene treatment, the number of Type III foci produced was about five-fold lower than in cultures treated with 3-methylcholanthrene alone. Therefore, PQ can inhibit Type III focus formation in C3H/10T1/2 cells. (Author abstract) (16 Refs)

30. MUTAGENICITY OF EXPERIMENTAL INHALATIONAL ANESTHETIC AGENTS: SEVOFLURANE, SYNTHANE, DIOXYCHLORANE, AND DIOXYFLURANE.

Baden JM, Kelley M, Mazze RI
Anesthesiology Service (112A), Veterans Admin. Medical Center, 3801 Miranda Ave., Palo Alto, CA, 94304
Anesthesiology; 56(6):462-463 1982

A modification of the Ames bacterial assay system employing two histidine-dependent strains of Salmonella typhimurium, TA1535 and TA100, was used to test the mutagenicity of four experimental, inhalational anesthetic agents: sevoflurane, synthane, dioxychlorane, and dioxyflurane. None of the anesthetics was mutagenic. Increased activity was seen only with vinylidene chloride, the positive control. (Author abstract) (3 Refs)

31. SISTER CHROMATID EXCHANGE INDUCED BY SHORT-LIVED MONOADDUCTS PRODUCED BY THE BIFUNCTIONAL AGENTS MITOMYCIN C AND 8-METHOXYPSORALEN.

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Environ Mutagen; 4(3):239-247 1982

To determine if DNA crosslinks are involved in the induction of sister chromatid exchange (SCE), Chinese hamster ovary cells were exposed to two bifunctional alkylating agents mitomycin C (MMC) and 8-methoxypsoralen (MOP), and their monofunctional derivatives decarbamoyl mitomycin C (dcMMC) and angelicin (ANG). With all the agents used, the av number of SCE/cell increased with increasing concentration. Both MMC and dcMMC had a similar effect in inducing SCE. MOP + UVA was more active in producing SCE than ANG + UVA. MMC and dcMMC were also very similar in the lifetime of lesions leading to SCE formation. MOP + UVA was remarkably similar to MMC and dcMMC in the lifetime of lesions leading to SCE formation. ANG + UVA, however, behaved in a different manner in that it caused longer-lived lesions in cells with comparable numbers of SCE. Thus, at the lowest concentration of ANG tested, the number of SCE produced during the second, as well as the first, cell cycle was increased. The elevated frequency of single SCE did not change as the concentration of ANG was increased. This behavior, like that of methanesulfonate, indicates that several different types of DNA lesions are capable of SCE induction. (35 Refs)

32. EFFECT OF NONOXYNOL-9, A DETERGENT WITH SPERMICIDAL ACTIVITY, ON MALIGNANT TRANSFORMATION IN VITRO.

Long SD, Warren AJ, Little JB
Lab. Radiobiology, Dept. Physiology, Harvard Sch. Public Health, Boston, MA, 02115
Carcinogenesis; 3(5):553-557 1982

The detergents nonylphenoxypoly(ethyleneoxy) ethanol (NP-9), Tween 60, Nonidet P-40, and Triton X-100 were analyzed in an in vitro transformation assay using mouse BALB/3T3 fibroblasts and mouse 10T1/2 fibroblasts. NP-9, which is a common ingredient in commercially available spermicides, induced a significant number of Type 3 foci in both mouse cell transformation systems. The other detergents were inactive in both cell systems. These findings, in light of recent human epidemiological data on the relation of vaginal spermicides to congenital disorders suggests the need for further evaluation of NP-9 for potential mutagenicity, carcinogenicity, and teratogenicity. (Author abstract) (20 Refs)

33. TETRACYCLINE-INDUCED MUTATION IN CULTURED CHINESE HAMSTER CELLS.

Bhattacharjee SB, Pal B
Biophysics Div., Saha Inst. Nuclear Physics, 37 Belgachia Road, Calcutta 700 037, India
Mutat Res; 101(4):329-338 1982

Induction of 8-azaguanine-resistant mutants in cultured Chinese hamster cells by treatment with tetracycline hydrochloride (TC), and the influence of ascorbic acid (AA) on such induction, is reported. Toxic effects of TC at various concentrations for a fixed treatment time of 48 hr, and at different treatment times at a fixed concentration of 50 ug/ml, were examined. Little cellular killing up to a concentration of 30 ug/ml was observed when treatment time did not exceed 48 hr. At a treatment time of 48 hr, TC at 50 ug/ml resulted in survival of approx 70%. A rapid loss of cellular viability was observed when the TC concentration exceeded 80 ug/ml or the treatment time exceeded 72 hr. The expression time varied from 0-8 days at TC concentrations of 50 and 30 ug/ml and treatment time of 48 hr. A gradual increase in the mutation frequency up to approx 5 days of expression, followed by a plateau in the yield at day 6 was observed. The general behavior pattern was the same for both concentrations of TC. A gradual rise in the yield of mutants with increasing concentrations was observed. Effects of AA (10 and 20 ug/ml) upon TC-induced killing and mutation frequency were examined at a treatment time of 48 hr. AA itself had no effect upon the viability of mutation. Pretreatment with AA did not influence TC-induced killing but significantly suppressed the yield of mutants. When TC treatment was immediately followed by AA treatment, an increase in the viable number and a decrease in the yield of mutants were observed. (25 Refs)

34. ANTI-TUMOR ALKYLATING AGENTS ACT SYNERGISTICALLY WITH METHYLXANTHINES ON INDUCTION OF SISTER-CHROMATID EXCHANGE IN HUMAN LYMPHOCYTES.

Mourelatos D, Dozi-Vassiliades, Granitsas A
Dept. General Biology, Faculty Medicine, Aristotelian Univ., Thessaloniki, Greece
Mutat Res; 104(4/5):243-247 1982

Combination of chlorambucil (CBC), melphalan (MEPH), cis-platinum(II) diamine dichloride (cis-PtII), and caffeine, and theophylline and diphylline alone and in combination with

CBC, MEPH, and cis-PtII were used upon normal human lymphocytes to determine sister-chromatid exchange (SCE). Results showed that when methylxanthine was added to the cultures exposed to an alkylating agent at doses sufficiently high to induce SCE, the effect of methylxanthine was synergistic, the SCE level being much higher than that expected by the simple addition of the effects of the agent and methylxanthine. Any methylxanthine alone at concentrations used throughout the experiments (100 ug/ml) induced only a small increase in SCE rates. The relative ability to potentiate the production of SCE induced by cis-PtII (100 nanog/ml) appeared to be: caffeine greater than theophylline greater than diphylline. The difference between the results on human lymphocytes and the findings on rodent material might be accounted for by the different cell types used. In cultured rodent cells, in which only a poor pre-replication repair system exists, caffeine interferes with post-replication repair, which may be responsible for the decrease observed in SCE frequency. (15 Refs)

35. REPAIR OF TRANS-PT(II)DIAMMINEDICHLORIDE DNA-PROTEIN CROSSLINKS IN NORMAL AND EXCISION-DEFICIENT HUMAN CELLS.

Fornace AJ, Seres DS
Lab. Pathology, NCI, NIH, Bethesda, MD, 20205
Mutat Res; 94(2):277-284 1982

Sensitivity of xeroderma pigmentosum (XP) group A fibroblasts to trans Pt(II)-diamminedichloride (trans-Pt) was studied to find out whether the repair of DNA-protein crosslinks (DPC) induced by trans-Pt was deficient in XP cells. DPC, produced in cells by trans-Pt, was measured by the alkaline elution technique. When the cells were treated with trans-Pt and exposed to 3 kilorads, the level of cross linking was very similar in both normal and XP cells. The level of DPC increased somewhat in both cell types in the first several hours after trans-Pt was removed. By 12 hr, the DPC level was significantly less in normal as compared to XP cells. By the 18 hr the DPC level was approx half the maximal in the normal cells but decreased little in XP cells. Trans-Pt alone induced a negligible level of DNA single strand breaks (SSB) in both cell types; cytosine arabinoside and hydroxyurea induced a small but consistent increase in elution. With the polymerase inhibitor and trans-Pt, a marked increase in elution was observed in normal but not XP cells. In order to determine if trans-Pt was more toxic to XP cells, colony survival experiments were preformed. Trans-Pt was more toxic to XP cells; a concentration of trans-Pt 3-4x greater was needed in normal cells to produce the same toxicity observed in XP cells. A similar result was also observed with CRL1187 cells. (17 Refs)

36. THE IN VITRO TERATOGENICITY OF CYCLOPHOSPHAMIDE IN RAT EMBRYOS.

Greenaway JC, Fantel AG, Shepard TH, Juchau MR
Central Lab. for Human Embryology, Dept. Pediatrics, RD-20, Univ. Washington, Seattle, WA, 98195
Teratology; 25(3):335-343 1982

Embryonic defects induced by cyclophosphamide (CP) in rat embryos in vitro and in vivo were compared. Characteristic malformations were induced by growing Day 10 embryos in culture containing CP, hepatic microsomal fraction (S-9), and cofactors for monooxygenation. Abnormalities included cephalic defects and anomalies of the limb bud, tail, and mandibular arch; decrements were seen in crown-rump length, somite number, and protein content. Histologically, embryos exposed to CP in vivo were not distinguishable from those exposed in vitro. The av protein content of embryos exposed in vitro to a constant level of CP (25 ug/ml) decreased with increasing concentrations of S-9 from animals pretreated with polychlorinated biphenyls (PCB: Aroclor 1254). Malformation incidence was more sensitive than av protein content to changes in S-9 concentration. S-9 prepared from phenobarbital-pretreated rats produced a high incidence of malformations in embryos exposed to CP and cofactors, while use of S-9 from methylcholanthrene-pretreated animals and the same concentration of CP and cofactors did not result in malformations. Metyrapone and carbon monoxide effectively reduced teratogenic activity generated with S-9 from PCB-pretreated rats. Addition of metyrapone significantly increased embryo growth relative to that seen after treatment with CP plus activation but no metyrapone. The presence of 10% CO and 10% O_2 also diminished the teratogenic effect but to a lesser extent than metyrapone. These findings support the idea that teratogenicity of CP is dependent upon one or more maternal P450 monooxygenase systems. (23 Refs)

37. COMPARISON OF THE MUTAGENICITY AND TERATOGENICITY OF CYCLOPHOSPHAMIDE AND ITS ACTIVE METABOLITES, 4-HYDROXYCYCLOPHOSPHAMIDE, PHOSPHORAMIDE MUSTARD, AND ACROLEIN.

Hales BF

Dept. Pharmacology and Therapeutics, McGill Univ., Montreal, Quebec H3G 1Y6, Canada

Cancer Res; 42(8):3016-3021 1982

Cyclophosphamide must be metabolically activated to have max mutagenic or teratogenic activity. The first step in this activation is hydroxylation to 4-hydroxycyclophosphamide; this metabolite breaks down to form two cytotoxic metabolites, phosphoramide mustard and acrolein. In this report, the mutagenicity and teratogenicity of cyclophosphamide, 4-hydroperoxycyclophosphamide (which forms 4-hydroxycyclophosphamide spontaneously in solution), phosphoramide mustard, and acrolein were compared. The activation of cyclophosphamide to mutagenic metabolites was dependent on the presence of liver microsomes and reduced nicotinamide adenine dinucleotide phosphate while both phosphoramide mustard and 4-hydroperoxycyclophosphamide were mutagenic without activation, with the latter being the most potent. The third metabolite, acrolein, was bacteriotoxic at low concentrations; it was not mutagenic in the absence and only very weakly mutagenic in the presence of liver microsomes. All four compounds tested were teratogenic. The malformations produced by cyclophosphamide, 4-hydroperoxycyclophosphamide, and acrolein included edema, hydrocephaly, open eyes, cleft palate, micrognathia, omphalocele, bent tail, and forelimb and hindlimb defects, whereas phosphoramide mustard produced only hydrocephaly and tail, forelimb, and hindlimb defects. 4-Hydroperoxycyclophosphamide and its breakdown product, acrolein, were more potent as teratogens than either cyclophosphamide or phosphoramide mustard. cyclophosphamide produced malformations in both the injected and contralateral uninjected fetuses while the other three compounds all produced malformations only in the injected fetuses. Thus, the site of activation of cyclophosphamide to a teratogen is probably maternal. Because acrolein plays a major role in the teratogenicity of cyclophosphamide but is only weakly, if at all, mutagenic, the teratogenicity and mutagenicity of metabolites of this drug are dissociable. (41 Refs)

38. BUTYLATED HYDROXYANISOLE AS A POSSIBLE MUTAGENIC AGENT.

Degre R, Saheb SA
Centre de Recherche en Bacteriologie, Institut Armand-Frappier, Universite du Quebec, C.P. 100, Laval-des-Rapides, Laval, Quebec H7N 4Z3, Canada
Fems Microbiol Lett; 14(3):183-186 1982

Evidence is presented that butylated hydroxyanisole (BHA) is possibly mutagenic for Staphylococcus aureus strain Wood 46. One wk after inoculation of S aureus into tubes containing 12.5 and 25 ug of BHA, growth occurred in 22 of 23 tubes. Subcultures from these tubes gave rise to many colonies that were similar to the resistant strain of S aureus (W-46R). Control tubes containing medium plus solvent (ethanol) did not support growth. (21 Refs)

REVIEWS AND OTHER COMPOUNDS

39. SURFACE ACTIVITY OF SOME TUMOUR PROMOTERS.

Boyland E, Mohiuddin J
TUC Inst. Occupational Health, London Sch. Hygiene and Tropical Medicine, London WC1E 7HT, England
IRCS Med Sci [Cancer]; 9(8):753-754 1981

Surface activities of some known tumor promoters and related compounds were determined. Compounds with little activity included urea, calcium acetate, sodium chloride, glycerol, sodium nitrilotriacetate, phenol and glucose. Those with moderate activity were sodium saccharin, sodium cyclamate, sodium phenobarbitone, and ethanol. Those with high surface activity included salts of bile acids and fatty acids and Tween 40. The relevance of these findings to tumor promotion in vivo is discussed. (16 Refs)

40. THEORETICAL POSSIBILITIES OF PREDICTING HARMFUL EFFECTS OF DIFFERENT CHEMICALS ON LIVE ORGANISMS..

Veljkovic V, Vojvodic V
Institut 'Boris Kidric', Beograd, Yugoslavia
Arh Hig Rada Toksikol; 32(4):311-319 1981

Theoretical possibilities of predicting harmful effects of different chemicals on live organisms are discussed reviewing previous studies. Mathematical equations that could be used for estimating the carcinogenic potential of organic chemicals are presented. Obtained results are compared with data on chemical carcinogenesis in experimental animals according to the International Agency for Research on Cancer in Lyon. One-hundred-sixty-six insecticides and 253 other bactericidal and fungicidal compounds were investigated. (12 Refs) (In SCR)

41. CARCINOGEN-MEDIATED AMPLIFICATION OF SPECIFIC DNA SEQUENCES.

Lavi S
Dept. Virology, Weizmann Inst. Science, Rehovot, Israel
J Cell Biochem; 18(2):149-156 1982

The development of a experimental system model , which utilizes simian virus 40 (SV40)-transformed Chinese hamster embryo cells, coupled with a highly sensitive in situ hybridization procedure for the detection of a single cell in which viral DNA synthesis has been induced, is presented. When exposed to chemical carcinogens such as benzo(a)pyrene, N-methyl-N'-nitro-N-nitrosoguanidine, 7,12-dimethyl benz(a)anthracene (DMBA), ethyl methanesulfonate aflatoxin B1, and 3-methylcholanthrene or physical carcinogens (gamma or UV radiation), SV40 DNA synthesis was induced in treated cells. Noncarcinogenic compounds such as phenanthrene and dibenz(a,c)anthracene had no effect. While carcinogen-induced amplification of SV40 DNA sequences is controlled by the viral 'A' gene, no infectious virus or complete SV40 DNA molecules were found in treated cells. DMBA treatment induced a heterogenous collection of DNA molecules with SV40 sequences. Analysis of Hirt's supernatant using restriction enzyme analysis of the amplified DNA molecules indicated that not all sequences in the integrated SV40 inserts are present. Amplification of SV40 DNA sequences may reflect a more general gene amplification phenomenon mediated by chemical carcinogens. (19 Refs)

42. STRUCTURE-ACTIVITY STUDIES ON THE MUTAGENICITY OF TRIS(2,3-DIBROMOPROPYL)PHOSPHATE (TRIS-BP) AND ITS METABOLITES IN SALMONELLA.

Zeiger E, Pagano DA, Nomeir AA
Lab. Molecular Genetics, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
Environ Mutagen; 4(3):271-277 1982

Five methylated metabolites of the flame retardant tris(2,3-dibromopropyl)phosphate (Tris-BP) were tested for mutagenicity in Salmonella typhimurium strains TA1535 and TA100. The metabolites tested produced a gradient of mutagenic responses in TA1535 in the same dose range and up to the same magnitude as the Tris-BP response. None appeared to be the ultimate mutagen, since all required the S-9 fraction. The loss of the first dibromopropyl group did not affect mutagenicity whereas loss of the next dibromopropyl group resulted in decreased mutagenicity. The loss of bromine and the addition of a double bond between carbons 2 and 3 further decreased mutagenicity. Trimethyl phosphate was mutagenic in strain TA100 both in the presence and absence of S-9. Tripropyl phosphate was not mutagenic at any of the doses tests in TA100 or TA1535, with or without S-9. A possible detoxification pathway for these compounds is discussed. (12 Refs)

43. REVERSIBLE BLOCKING OF MYOGENESIS BY A CHEMICAL CARCINOGEN (MEETING ABSTRACT)

Parker A, Holtzer H
Department of Anatomy, University of Pennsylvania, Philadelphia, PA
Anat Rec; 202(3):8A 1982

EMS (ethyl methanesulfonate), a chemical carcinogen and a mutagen, reversibly blocks the synthesis and assembly of muscle-specific proteins into striated myofibrils; it does not block the synthesis or assembly of the muscle-specific, 10nm, intermediate-sized filaments (MIF). One hundred percent of day 4 myotubes in control cultures displayed normal striated myofibrils. Striated myofibrils were either totally absent or greatly reduced in number in day 4 myotubes that had been treated with EMS for the last 72 hours of culture. The presence of myofibrils was determined by fluorescein-labelled anti-LMM, anti-alpha-actinin, anti-MIF and EM. Myotubes in both day 4 control and day 4 EMS-treated cultures displayed longitudinally-oriented MIF. The multinucleated structures that formed in EMS were atypical in over-all morphology. If the EMS-blocked myotubes were shifted to normal medium for an additional 3 days, they preceeded to assemble large numbers of striated myofibrils, in addition to assembling longitudinally-oriented MIF. Total mRNAs were translated in a rabbit in reticulocytelysate system from cultures that had been treated with EMS for 3 days and from cultures that had been allowed to recover for 3 days. Following separation of the in vitro synthesized labeled proteins in SDS-PAGE (sodium dodecyl sulfate-polyacrylamide gel electrophoresis), the fluorograms revealed that the mRNAs from myotubes in EMS for 3 days though translating MIF failed to translate detectable myosin heavy chains. The mRNAs from the recovered myotubes translated both myosin heavy chains and MIF. (no Refs)

44. MUTAGENICITY TESTS AND IN VITRO TRANSFORMATION ASSAYS ON TRIETHANOLAMINE.

Inoue K, Sunakawa T, Okamoto K, Tanaka Y

Biological Res. Section, Tochigi Res. Laboratories, Kao Soap Co., Ltd., 2606, Akabane, Ichikaimachi, Hagagun, Tochigi 321-34, Japan

Mutat Res; 101(4):305-313 1982

The mutagenicity and cell-transforming activities of triethanolamine were examined by measuring induction of DNA damage in Bacillus subtilis, mutagenicity in Salmonella typhimurium and Escherichia coli, production of chromosomal aberrations in Chinese hamster cells, and transformation of hamster embryo cells. Diethanolamine and monoethanolamine were also examined for induction of transformation. The results suggest that triethanolamine may not produce genotoxic effects by reaction with DNA and consequent induction of changes in DNA structure and function. The increased incidence of tumors induced in female mice by triethanolamine may be a secondary or indirect result of some specific cytotoxic effect. (20 Refs)

45. DEACYLATION OF 12-O-[3H]TETRADECANOYLPHORBOL-13-ACETATE AND [3H]PHORBOL-12,13-DIDECANOATE IN HAMSTER SKIN AND HAMSTER CELLS IN CULTURE.

Barrett JC, Brown MT, Sisskin EE
Environmental Carcinogenesis Group, Lab. Pulmonary Function and Toxicology, Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709
Cancer Res; 42(8):3098-3101 1982

The deacylation of tritium-labeled 12-O-tetradecanoylphorbol-13-acetate ([3H]TPA) and tritium-labeled phorbol-12,13-didecanoate ([3H]PDD) by hamster cells in culture and hamster skin in vivo was studied. Cell cultures of Syrian hamster embryo fibroblasts and preneoplastic or neoplastic derivatives of these cells deacylated [3H]TPA rapidly, and the major product observed cochromatographed on silica gel thin-layer chromatographs with phorbol-13-acetate. [3H]PDD was more stable under the same conditions although some radioactivity corresponding to phorbol-12-decanoate was observed. Cultures of dermal fibroblasts and epidermal cells from 1-day-old hamster deacylated [3H]TPA to phorbol-13-acetate but at a slower rate than observed with Syrian hamster embryo cells. [3H]PDD was also more stable than was [3H]TPA in these cultures, but the difference between the stability of these two phorbol ester derivatives was less pronounced in the presence of skin cells than in the presence of embryo cells. In contrast to the degradation of [3H]TPA and [3H]PDD observed by cells in culture, no deacylation on the phorbol diesters in intact hamster skin was detected. The compounds were cleared from hamster skin at a rate comparable to that observed in mouse skin. The radioactivity extracted from hamster skin for up to 48 hr after treatment appeared to be unchanged TPA or PDD. Pretreatment of hamster skin with 50 ug of TPA twice per wk for 4 wk did not alter the rate of clearance or the deacylation of [3H]TPA. These results indicate that hamster cells in culture can deacylate phorbol diesters, but in intact hamster skin, the rate of deacylation of TPA or PDD is not measurably different from that of mouse skin. These findings do not support the concept that the lack of TPA-induced tumor promotion in hamsters is due to metabolic inactivation of the promoter. (Author abstract) (20 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICITY OF POLYBROMINATED BIPHENYLS (PBBS) IN DOMESTIC AND LABORATORY ANIMALS.
Damstra T, Jurgelski W, Posner HS, Vouk VB, Bernheim NJ, Guthrie J, Luster M, Falk HL
Natl. Inst. Environmental Health Sciences, Post Office Box 12233, Research Triangle Park, NC, 22709
Environ Health Perspect; 44():175-188 1982

2. CHLOROFORM: A REVIEW OF ITS METABOLISM, TERATOGENIC, MUTAGENIC, AND CARCINOGENIC POTENTIAL.
Davidson IW, Sumner DD, Parker JC
(c/o Parker) ECAO, Environmental Protection Agency, MD-52, Research Triangle Park, MD, 27711
Drug Chem Toxicol; 5(1):1-87 1982

3. FORMALDEHYDE IN PRESENT-DAY ENVIRONMENTAL TOXICOLOGY.
Beritic T, Kovac S, Dimov D
Odjel za profesionalne bolesti, Institut za medicinska istrazivanja i medicinu rada, Zagreb, Yugoslavia
Arh Hig Rada Toksikol; 32(4):363-395 1981
In SCR

4. HORMONES AS ETIOLOGICAL AGENTS IN NEOPLASIA.
Furth J
Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

5. CURRENT VIEWS ON HORMONES AND BREAST CANCER.
Molinatti GM, Limone P
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Minerva Med; 73(17):1047-1053 1982
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6. THE CHROMOSOMAL EFFECTS OF THE ORAL CONTRACEPTIVE.
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J Surg Oncol; 20(2):115-118 1982

7. TOXICITY AND CARCINOGENICITY OF NICKEL AND ITS COMPOUNDS. A REVIEW OF THE CURRENT STATUS.
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8. HISTORICAL OVERVIEW OF NITROSOUREA DEVELOPMENT.
Goldin A
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INSERM Symp; 19:3-11 1981

9. PATHOLOGY.
Goyer RA
Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC
JAMA; 247(21):2973-2975 1982

RADIATION CARCINOGENESIS

10. IDENTIFYING THE HEALTH RISKS FROM VERY LOW-DOSE SPARSELY IONIZING RADIATION.
Dreyer NA, Friedlander E
Epidemiology Resources, Inc., P.O. Box 57, Chestnut Hill, MA, 02167
Am J Public Health; 72(6):585-588 1982

11. RISK OF RADIOLOGICAL EXAMINATIONS.
Jankowski J
Instytut Medycyny Pracy w Lodzi, ul. Olowiana 6, 91-614 Lodz, Poland
Pol Przegl Radiol; 45(6):383-386 1981
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12. RADIOBIOLOGY OF RISK ESTIMATES IN MEDICAL IRRADIATION (MEETING ABSTRACT)
Rossi HH
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IN: 148th National Meeting of the American Association for the Advancement of Science, January 3-8, 1982, Washington, D.C. American Association for the Advancement of Science 182 pp., 1982.

13. RADIATION-INDUCED VASCULAR INJURY AND ITS RELATION TO LATE EFFECTS IN NORMAL TISSUES.
Law MP
MRC Cyclotron Unit, Hammersmith Hosp., London W12 OHS, England
Adv Radiat Biol; 9:37-73 1981

14. CURRENT CONCEPTS IN ULTRAVIOLET CARCINOGENESIS.
Granstein RD, Sober AJ
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15. METABOLIC CHANGES AFTER EXPOSURE TO RADIONUCLIDES.
Kalistratova VS
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Med Radiol (Mosk); 27(4):62-71 1982
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16. CAFFEINE: AN UPDATE.
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EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

18. RADIATION EPIDEMIOLOGY (MEETING ABSTRACT)
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148th National Meeting of the American Association for the Advancement of Science, January 3-8, 1982, Washington, D.C. American Association for the Advancement of Science 182 pp., 1982.

19. EPIDEMIOLOGICAL STUDIES ON RADIATION CARCINOGENESIS IN HUMAN POPULATIONS FOLLOWING ACUTE EXPOSURE: NUCLEAR EXPLOSIONS AND MEDICAL RADIATION.
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20. EPIDEMIOLOGIC APPROACH TO CANCER.
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Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

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22. METABOLIC EPIDEMIOLOGY OF LARGE BOWEL CANCER.
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23. EPIDEMIOLOGY OF GASTRIC CANCER AND ITS PRECURSOR LESIONS.
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24. TRENDS IN THE INCIDENCE OF GASTRIC CARCINOMA (MEETING ABSTRACT)
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27. HOST AND ENVIRONMENTAL FACTORS ENHANCING CARCINOGENESIS IN THE RESPIRATORY TRACT.
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29. OCCUPATIONAL EXPOSURES TO URANIUM: PROCESSES, HAZARDS, AND REGULATIONS.
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Occupational Exposures to Uranium: Processes, Hazards, and Regulations. Available from National Technical Information Service, Springfield, VA, as PNL-3341-USUR-01:, 91 pp., 1981.

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30. THE ROLE OF RADIATION AND CHEMICALS IN THE INDUCTION OF MUTATIONS AND EPIGENETIC CHANGES DURING CARCINOGENESIS.
Trosko JE, Chang CC
Dept. Human Development, Coll. Human Medicine, Michigan State Univ., East Lansing, MI, 48824
Adv Radiat Biol; 9:2-36 1981

31. SOME EFFECTS OF CARCINOGENS ON CELL ORGANELLES.
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Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

32. CHEMICAL CARCINOGENESIS: INTERACTIONS OF CARCINOGENS WITH NUCLEIC ACIDS.
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Ludlum DB, Tong WP
Div. Oncology, Dept. Pharmacology and Experimental Therapy, Albany Medical Coll., Albany, NY, 12208
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35. CALMODULIN AND CA2+ IN NORMAL AND TRANSFORMED CELLS.
Veigl ML, Sedwick WD, Vanaman TC
Dept. Microbiology and Immunology, Duke Univ. Medical Center, Durham, NC, 27710
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Dept. Environmental Toxicology, Univ. California, Davis, Davis, CA, 95616
Adv Exp Med Biol; 136(partB):847-863 1982

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Lenk W, Scharmer U
Pharmakologisches Institut, Universitat Munchen, Nussbaumstrasse 26, D-8000 Munchen 2, W. Germany
Adv Exp Med Biol; 136(partB):951-970 1982

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Henschler D, Hoos R

Inst. Toxicology, Univ. Wurzburg, Versbacher Strasse 9, Wurzburg D-8700, W. Germany

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Reynolds ES, Moslen MT

Chemical Pathology Lab., Dept. Pathology, Univ. Texas Medical Branch, Galveston, TX

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van Bladeren PJ, Breimer DD, Rotteveel-Smijs GM, Hoogeterp JJ, Mohn GR, De Groot A, Van Zeeland AA, Van der Gen A

Dept. Pharmacology, Univ. Leiden, P.O. Box 9502, 2300 RA Leiden, The Netherlands

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Juchau MR, Chao ST, Namkung MJ

Dept. Pharmacology, Sch. Medicine, SJ-30, Univ. Washington, Seattle, WA, 98195

Adv Exp Med Biol; 136(partA):555-573 1982

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42. THE INTESTINAL ENZYMATIC BIOTRANSFORMATION SYSTEM: POTENTIAL ROLE IN PROTECTION FROM COLON CANCER.

Hoensch HP, Hartmann F

Medizinische Universitatsklinik, D-7400 Tubingen, W. Germany

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Rigby PW

Imperial Coll. Science and Technology, London SW7 2BZ, England

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Ichida F, Honma A, Soga K

Third Dept. Internal Medicine, Niigata Univ. Sch. Medicine, Niigata, Japan

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Walsh JW, Zimmer SG, Perdue ML

Div. Neurosurgery, Univ. Kentucky Medical Center, 800 Rose St., Lexington, KY, 40536

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46. TRANSLATION OF PHARMACOKINETIC/BIOCHEMICAL DATA INTO RISK ASSESSMENT.

Dietz FK, Reitz RH, Watanabe PG, Gehring PJ

Toxicology Res. Lab., Health and Environmental Sciences, Dow Chemical, 1803 Building, Midland, MI, 48640

Adv Exp Med Biol; 136(partB):1399-1424 1982

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Ward JM, Rice JM

Frederick Cancer Research Center, Frederick, MD

Second Annual Meeting of the Society of Environmental Toxicology and Chemistry, November 22-25, 1981, Arlington, Virginia. Society of Environmental Toxicology and Chemistry 150 pp., 1982.

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Egan H, Fishbein L, O'Neill IK, Castegnaro M, Bartsch H

Lab. Government Chemist, London, England

IARC Sci Publ (40): 347 pp., 1981.

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HYDRAZINES AND RELATED COMPOUNDS

1. DOSE RESPONSE CARCINOGENESIS BY 1,2-DIMETHYLHYDRAZINE DIHYDROCHLORIDE (MEETING ABSTRACT).

Toth B
Eppley Institute, University of Nebraska Medical Center, Omaha, NE, 68105
Fed Proc; 41(3):446 1982

The goal of the work was to reveal whether the carcinogenic effects of 1,2-dimethylhydrazine dihydrochloride (1,2-DMH) administered continuously for life to Swiss mice were dose-related. Therefore, 1,2-DMH was given in drinking water from 6 weeks of age for life to mice at the following dose levels: group 1, 0.002; group 2, 0.001; group 3, 0.0005; group 4, 0.00025; group 5, 0.000125; group 6, 0.0000625; group 7, 0.00003125 and group 8, 0.000015625%. Each group consisted of 100 mice (50 female, 50 male). The tumor incidences in the blood vessels and lungs due to treatment were as follows: group 1, 79 and 26%; group 2, 95 and 34%; group 3, 91 and 27%; group 4, 61 and 16%; group 5, 23 and 29%; group 6, 9 and 14%; group 7, 6 and 24%; and group 8, 1 and 32%, re-

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spectively. Evaluation of the findings indicates that with the exception of the highest dose, which was too toxic, a consistent increase in the dose level of 1,2-DMH was directly related to an increased incidence of blood vessel tumors. The data also showed that there was no association between the dose of the chemical and the lung tumor incidence. Interestingly, 1,2-DMH was without carcinogenic effect in the intestinal tract. The study is apparently the first attempt to perform a dose response inquiry with this powerful, widely used chemical carcinogen. (no Refs)

2. HYDROXYLATION AND ACTIVATION OF CARCINOGENS BY HUMAN COLON AND HUMAN COLON TUMOR CELLS (MEETING ABSTRACT).

Newaz SN, Fang WF, Strobel HW
The University of Texas Medical School, Houston, TX, 77025
Fed Proc; 41(3):1564 1982

Microsomes prepared from human colons obtained at autopsy catalyze the hydroxylation of benzo[a]pyrene (BAP) and 1,2-dimethylhydrazine (DMH). The metabolism of DMH was highest in microsomes prepared from the descending colon, intermediate in the transverse colon and lowest in the ascending colon. The metabolism of BAP does not show such an anatomical distribution. Human colon tumor cell line LS174T microsomes also catalyze the hydroxylation of DMH and BAP in an inducible manner. Phenobarbital/hydrocortisone (P/H) induces DMH hydroxylation 3-fold and BAP hydroxylation 10-fold. Benzanthracene (BA) induces BAP hydroxylation 30-fold indicating that these cells have a mixed function oxidase system. Cyclophosphamide (CP) is also hydroxylated to its cytotoxic metabolite by the colon tumor cells as judged by a 33% decrease in cell number. BA induces cyclophosphamide activation and cell killing by 80%, while P/H effects a 76% decrease in cell number as compared with controls. These results show that human colon and human colon tumor cells are totipotent for activation of carcinogens and the antitumor agent cyclophosphamide. (no Refs)

3. DIETARY PROTEIN CONCENTRATION AND THE METABOLISM OF 1,2-DIMETHYLHYDRAZINE BY MICE.

Karl FW
University of Illinois at Urbana-Champaign, Urbana, IL
Diss Abstr Int [B]; 42(9):3636-B 1982

At concentrations ranging from 2.5 to 10 mM, 1,2-dimethylhydrazine (DMH) and azoxymethane (AOM) did not increase the mutation frequency of Salmonella typhimurium (Strain G-46) in vitro. Murine liver microsomes and cofactors caused a 40-fold increase in mutation frequency with dimethylnitrosamine (DMN) but not with DMH or AOM in vitro. Methylazoxymethanol (MAM) was mutagenic in vitro without activation by liver preparations. The conversion of DMH, AOM, and MAM to mutagens was studied in growing male B6C3F1 mice fed isocaloric, semipurified casein, sucrose:dextrin diets containing 2.5, 5, 10, 20, or 40% protein. Mutagen formation from DMH and MAM varied slightly with diet but from AOM was directly proportional to dietary protein concentration. The percent of [14C]-DMH expired as a promutagen by growing mice fed 2.5, 10, or 40% protein was 63 +/-4, 44 +/-3, and 38 +/-3. The metabolism of DMH to mutagenic endproducts by mice was rate-limited by the conversion of azomethane to AOM and at least partially carried out by the liver. Increasing protein intake increased the bioactivation of DMH, AOM, and MAM and 2.5% protein diets caused greater expiration of promutagens from DMH, thereby decreasing the body burden of retained carcinogen. (no Refs)

4. EFFECT OF DIET ON THE METABOLISM OF 1,2-DIMETHYLHYDRAZINE (DMH) IN THE RAT (MEETING ABSTRACT).

Glauert HP, Bennink MR
Michigan State University, East Lansing, MI, 48824
Fed Proc; 41(3):356 1982

Dietary fat and liver have been shown to influence DMH-induced colon carcinogenesis in experimental animals. One possible mechanism is that diet alters DMH metabolism. In this experiment, we examined the effect of dietary fat, wheat bran, and agar on 1) the metabolism of DMH to products which bind to DNA in rat colon epithelial cells (CEC), and 2) the clearance of DMH and its metabolites from blood. Diets were fed for four weeks; labeled DMH was then injected ip and rats were killed at various time intervals (12-96 hours). CEC were isolated from the colon and DNA was purified from CEC. Maximum binding DMH metabolites to DNA was seen 36 hours after the injection of DMH. The amount of 14C binding to DNA was not altered by diet but a diurnal variation was evident. Maximum 14C binding at 9 pm was 32-109% greater than 14C binding at 9 am. Serum radioactivity was greater in rats fed the high-fat diet and lower in rats fed the wheat bran compared to the control group. 14C disappearance from serum fit a 'two-pool model' with half-life for the first pool ranging from 27 to 33 hr and half-life for the first pool ranging from 62 to 71 hr; diet did not alter half-life for either pool. This experiment shows that diet does not alter the amount of DMH metabolites bound to DNA in CEC even though diet does change the level of DMH plus its metabolites in serum. It appears that there is a marked diurnal variation in DMH metabolism. (no Refs)

5. INDUCTION OF COLON MUCOSAL B-GLUCURONIDASE PRODUCTION AS A MECHANISM FOR 1,2-DIMETHYL-HYDRAZINE COLON SPECIFICITY (MEETING ABSTRACT).

Celik C, Lewis DA, Paloini NS, Holyoke ED
Roswell Park Memorial Institute, Buffalo, NY, 14263
Proc Am Assoc Cancer Res; 23:324 1982

Although early studies in germ free rats showed almost complete dependence of dimethylhydrazine (DMH) colon carcinogenesis upon the presence colon bacteria, no adequate explanation was given for the 20% tumor incidence observed in germ free animals. Bacterial activation of liver microsomal products releasing active proximate carcinogens has been the accepted reason for the exquisite specificity DMH has for the colon. Recent work, including the present study, show the colon mucosa is capable of metabolizing carcinogens and activating conjugated forms metabolized in the liver independent of the intestinal microflora. Mucosal B-glucuronidase production was assayed in coded, scraped mucosa samples from the duodenum/jejunum, ileum, right colon, and left colon of normal and DMH treated rats. Normal mucosal B-glucuronidase production was highest in the left colon followed by the right colon, duodenum, and ileum respectively. Enzyme production in the left colon was significantly increased 24 hours after injection of 25mg/kg body weight DMH. No elevation was seen in other mucosal samples. Metabolism of DMH to oxidated forms conjugated to glucuronic acid is well established. Thus, this study offers a possible role for carcinogen induction of a metabolic enzyme in its target tissue. (no Refs)

6. POTASSIUM INHIBITION OF 1,2-DIMETHYLHYDRAZINE-INDUCED COLON CARCINOGENESIS (MEETING ABSTRACT).

Jacobs MM

Eppley Institute for Research in Cancer, University of Nebraska Medical, Center Omaha, NE, 68105

Proc Am Assoc Cancer Res; 23:345 1982

A reduction in the 1,2-dimethylhydrazine (DMH)-induced colon tumor incidence by potassium in Sprague Dawley (SD) rats is demonstrated. Male SD rats were injected weekly with 20 mg DMH/kg body weight for 20 weeks. Potassium supplemented drinking water was initiated 1 week before the first DMH treatment and was continued until sacrifice 14 weeks after the last DMH treatment. Rats provided 0.5% K (potassium chloride) in the drinking water and Wayne Lab-blox diet were ingesting 2-fold more potassium than the unsupplemented controls. At sacrifice the incidence of DMH-induced colon tumors was significantly reduced to 70% (12/17) with the potassium additive compared to 100% (13/13) in the DMH controls receiving no supplemental potassium. Potassium also reduced the mean diameter of the tumors and appeared to shift the location of the tumors from the proximal to the transverse and distal colon. The predominant extracolonic tumors induced by DMH were ear duct, pancreatic and small intestine. All were reduced by potassium. Survival was better in potassium plus DMH treated rats (85%) than in the DMH only control (65%). At the level tested potassium did not affect the weight gain of the animals. The reduction in colon tumor incidence may be due to potassium inhibition of DMH activation, enhancement of DMH detoxification or to modification of other cellular processes associated with DMH carcinogenesis. (no Refs)

7. HYPERPLASIA AND HYPERPLASTIC POLYPS IN THE LARGE INTESTINE OF MICE DURING 1,2-DIMETHYLHYDRAZINE-INDUCED CARCINOGENESIS.

Krutovskikh VA

All-Union Cancer Res. Center, Moscow, USSR

Eksp Onkol; 4(3):20-25 1982

Development and potential malignant transformation of hyperplastic polyps of the large intestine were studied in male (CBA x C57BL)F1 mice exposed to 1,2-dimethylhydrazine (DMH: 16 mg/kg/wk, sc). Within different time periods after the initiation of DMH administration, the mice were sacrificed, and specimens of large intestine were subjected to scanning electron microscope examination. The DMH administration resulted in progressive changes in the ultrastructure of crypts. Hyperplastic exophytic nodules were first detected 10-15 wk after the initiation of the experiment. The number of nodules correlated with the degree of hyperplasia of the intestinal mucosa. Approx 5-10% of the hyperplastic polyps showed malignant transformation; spherical or saucer-like tumors with foci of tissue atypia were first detected after 20-wk administration of the DMH. All tumors observed after 25-30-wk administration infiltrated the intestinal wall. (14 Refs) (In RUS)

8. PERIANAL LESIONS OF BALB/C MICE INDUCED BY 1,2-DIMETHYLHYDRAZINE DIHYDROCHLORIDE AND METHYLAZOXYMETHANOL-ACETATE: THEIR CLASSIFICATION AND HISTOGENESIS.

Kumagai H, Kawaura A, Furuya K, Izumi K, Otsuka H

Second Dept. Pathology, Sch. Medicine, Univ. Tokushima, Kuramoto-cho 3-18-15, Tokushima 770, Japan

Gan; 73(3):358-364 1982

The histogenesis of perianal squamous cell carcinomas induced by subcutaneous and intraperitoneal injection of 1,2-dimethylhydrazine dihydrochloride (DMH) and painting of methylazoxymethanol (MAM)-acetate on the anal region was investigated in 212 female BALB/c mice. Painting of MAM-acetate and injection of DMH induced similar benign and malignant tumors and hyperplastic lesions in the anal region. In chronological studies on animals given DMH subcutaneously, cystic or solid squamous lesions, foci of immature sebocytes, sebaceous hyperplasias and sebaceous adenomas were identified. These lesions seemed to be precursors of carcinomas that developed in the same region, and originated from hair follicles or sebaceous glands of the pilosebaceous complexes, but not from the anal mucosa. In mice treated with DMH, the incidence of perianal carcinomas was high in groups with high incidences of colon carcinomas. (Author abstract) (18 Refs)

9. EFFECT OF DIETARY FAT AND ANTIOXIDANT ON INCIDENCE OF SPONTANEOUS AND 1,2-DIMETHYLHYDRAZINE-INDUCED TUMORS IN MICE (MEETING ABSTRACT).

Brown RR, Erturk E, Arend RA, Potera C, Remus N, Ruzicka E, Dallmann L

University of Wisconsin Center for Health Sciences, Madison, WI, 53792

Proc Am Assoc Cancer Res; 23:277 1982

In attempts to further define the role of type and quantity of dietary fat and antioxidants on cancer incidence, we studied tumor incidence (spontaneous and dimethylhydrazine (DMH) induced) in mice fed semipurified diets having one of 5 different vegetable fat mixes containing respectively 59% saturated (SAT), 60% monoene (MUF), 59% diene (DUF), 35% trans-monoene (TRN), or 4% triene (TUF). Butylatedhydroxyanisole (BHA) was added to some SAT and TUF diets. Weanling CD-1 mice of both sexes (40/group) and female C3H (60/group) were fed these diets having 5% or 17% fat substituted isocalorically for sucrose. Treated mice received 10 weekly subcutaneous injections of 0.25 mg DMH freshly neutralized. Controls received buffer only. DMH caused liver tumors and a few kidney and lung tumors and splenic leukemia, but no colon tumors. More DMH-induced liver and lung tumors were seen in males fed 5% TRN than in other groups but this was not confirmed in males fed 17% TRN. Total tumors in males fed 17% and 5% fats were not different suggesting that when fed isocalorically, the quantity of fat did not influence tumor incidence in CD-1 males. BHA reduced the DMH-liver tumor rate in 17% SAT but not in 17% TUF. DMH-liver tumors were fewer in 17% SAT than in 17% TUF males and this difference was even greater between SAT+BHA+DMH and TUF+BHA+DMH groups. (no Refs)

10. EFFECTS OF DIMETHYLHYDRAZINE TREATMENT AND FEEDING REGIMEN ON CELL PROLIFERATION IN THE RAT DESCENDING COLON (MEETING ABSTRACT).

Heitman W, Cameron IL

The University of Texas Health Science Center, San Antonio, TX, 78284

Proc Am Assoc Cancer Res; 23:269 1982

The purpose of this study was to test for interactions between 1,2-dimethylhydrazine (DMH) treatment and feeding regimen on rat colonic epithelium. Rats were given 8 weekly injections of DMH (9.5 mg/kg body wt) which induced an irreversible preneoplastic state of the colonic epithelium. Control rats were injected with the same volume of vehicle solution. At the end of the treatment period, rats were placed on one of three different isocaloric feeding regimens for 10 days: solid food ad libitum, a complete liquid elemental diet given ad libitum, or total parenteral nutrition with the same complete elemental diet (TPN). Three hours prior to killing the rats, each rat received an ip injection of colchicine at a dosage of 1 mg/kg body wt. Cell proliferative parameters were measured in the descending colon. These data were subjected to a two-way analysis of variance. The oral administration of the solid and liquid diets, regardless of chemical constituents, supported the DMH-induced increase in colonic epithelial cell proliferation. TPN did not support this DMH-induced increase in the proliferative zone metaphase index. This differential influence on cell proliferation in DMH-perturbed epithelium can be attributed to the intravenous administration of the liquid diet compared to the oral administration of the liquid diet or the solid diet. Thus, route of administration has a significant influence on the preneoplastic colonic epithelium. (no Refs)

11. CARCINOGEN-INDUCED DNA DAMAGE AND CELLULAR ALTERATIONS IN F344 RAT COLON ORGAN CULTURES.

Telang NT, Williams GM

(c/o Williams) Div. Pathology and Toxicology, Naylor Dana Inst. Disease Prevention, American Health Foundation, Dana Road, Valhalla, NY, 10595

JNCI; 68(6):1015-1022 1982

Optimized culture conditions were used to achieve prolonged survival of colon mucosa from conventional inbred F344 strain rats. Up to 21 days in culture, a high percentage of explants had viable mucosa with intact crypt columns and maintained active replicative DNA synthesis in the proliferative zone of the crypts. An acute 4-hr in vitro exposure to 0.5 mM of the colon-selective carcinogens 1,2-dimethylhydrazine dihydrochloride (DMH) and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) produced 26 and 78% suppressions of replicative DNA synthesis, respectively, whereas the same exposure to the liver carcinogen dimethylnitrosamine produced only a 5% suppression. the thymidine-labeling index of DMH-exposed cells was lower than that of control cells at 1 day and then increased above the control values 7-21 days later. MNNG exposure produced pronounced morphologic changes in the crypt columns. MNNG-exposed cultures that were transplanted into the mammary fat pads of syngeneic female rats produced hypercellular cysts different from those formed by nonexposed fragments. These findings indicate that the acute and persistent effects of colon carcinogens can be studied directly on the target tissue in organ cultures. (Author abstract) (46 Refs)

12. EFFECT OF ETHIONINE ON SAM METABOLISM AND DNA METHYLATION IN HYDRAZINE-TREATED RATS (MEETING ABSTRACT).

Barrows LR, Shank RC, Magee PN

Fels Research Institute, Temple University, Philadelphia, Pa, 19140

Proc Am Assoc Cancer Res; 23:206 1982

Radioactive 7-methylguanine (7MG) and O6-methylguanine have been detected in liver DNA of rats treated with radioactive methionine and hepatotoxic doses of hydrazine. We have recently shown S-adenosylmethionine (SAM) to methylate DNA directly to produce these same derivative bases. In an attempt to determine if DNA methylation could be modulated by interfering with SAM metabolism, SAM levels, specific activity, and DNA methylation were monitored in hydrazine-treated rats also receiving ethionine. In rats treated with 500mg ethionine/kg 12 hours before administration of hydrazine (60mg/kg) and [3H]methionine (100uCi/hour, for 5 hours) no inhibition of 7MG formation was observed. SAM levels in these animals were slightly below normal, SAM specific activity was normal. Liver S-adenosylethionine concentrations at this time were 2umoles/g liver wet wt, normal SAM concentrations were 65nmoles/g liver wet wt. However, in rats treated with [3H]methionine (300uCi), ethionine (500mg/kg), and hydrazine (60mg/kg) at 15 min intervals, no 7MG was detected. In these rats liver SAM levels fell to 25% of normal within 15 min of ethionine administration. 7MG was detected in the DNA of rats receiving only [3H]-methionine and hydrazine. 5-Methylcytosine synthesis was not inhibited in rats treated with ethionine and hydrazine, and was increased in rats receiving ethionine 15 min before hydrazine. (no Refs)

HETEROCYCLIC COMPOUNDS

13. MUTAGENESIS BASED ON DEPURINATION BY CHEMICAL CARCINOGENS (MEETING ABSTRACT).

Loeb LA, Schaaper RM, Kunkel TA

Gottstein Memorial Cancer Research Laboratory, SM-30, University of Washington, Seattle, WA, 98195

Proc Am Assoc Cancer Res; 23:254 1982

An analysis of apurinic sites as an intermediate in mutagenesis by chemical carcinogens has been carried out. Alkylation of the N-3 and N-7 positions on purines in DNA causes cleavage of the bond between the base and sugar yielding apurinic sites. Copying of DNA containing apurinic sites by DNA polymerases in vitro results in enhanced mis-incorporations. Transfection of phix174 DNA containing apurinic sites results in mutagenesis when assayed in Escherichia coli spheroplasts expressing error-prone DNA repair. We measured the infectivity and mutagenicity of phix DNA treated with beta-propiolactone (BPL), benzo(a)pyrene diolepoxide, and N-acetoxy acetylaminofluorene. With each compound, mutagenicity is dependent on the induction of the error-prone pathway. Heating of DNA treated with BPL causes alkaline labile (presumably apurinic) sites and concomitantly an increase in mutagenicity. The reversion frequency of untreated amber 86 DNA is 12 X 10(-6), after treatment with BPL it increases to 25 X 10(-6) and exposure of the BPL treated DNA to elevated temperature results in a further increase to 185 X 10(-6). The increase in mutagenicity is proportional to the number of alkaline labile sites introduced and is in agreement with the mutagenic potential of apurinic sites. These results suggest a model in which bulky adducts terminate DNA replication and induce alterations in the DNA replicating complex. (no Refs)

14. REVERSAL OF CYTOSOLIC INHIBITION OF NUCLEAR AND MICROSOMAL MEDIATED BINDING OF AFLATOXIN B1 (AFB1) TO DNA BY EPOXIDES (MEETING ABSTRACT).

Lotlikar PD, Jhee EC, Clearfield MS, Paik SM, Pandey RN
Department of Biochemistry, Fels Research Institute, Temple University Medical School, Philadelphia, PA, 19140
Proc Am Assoc Cancer Res; 23:364 1982

Involvement of hepatic GSH S-transferases is indicated by cytosolic inhibition of nuclear and microsomal mediated binding of AFB1 to DNA. We have now examined effects of 1mM levels of trichloropropene oxide (TCPO) and styrene oxide (SO) on this inhibition process. Intact rat and hamster liver nuclei, microsomes and cytosols were used for these studies. Radioactivity present in DNA isolated by a modified Marmur procedure indicated AFB1 binding to DNA. With hamsters, 250 pmoles of [3H]AFB1 were bound to calf thymus DNA in the microsome mediated assay. Presence of either TCPO or SO did not have any stimulatory effect on this binding. Cytosol inhibited the microsome mediated AFB1-DNA binding by 70%. However, presence of either TCPO or SO reversed the cytosolic inhibition completely. In separate experiments, SO also inhibited the formation of AFB1-GSH conjugate. Intact nuclei formed 40-80 pmoles of [3H]AFB1 bound to endogenous DNA with or without microsomes. Presence of cytosol inhibited this binding by 80%. Addition of either epoxide reversed the cytosolic inhibition completely. These epoxides produced similar effects with rat liver fractions. These results provide additional evidence that GSH S-transferases are involved in cytosolic inhibition of nuclear and microsomal mediated AFB1 binding to either exogenous or endogenous DNA. (1 Ref)

15. ROLE OF DEPURINATION IN MUTAGENESIS BY CHEMICAL CARCINOGENS.

Schaaper RM, Glickman BW, Loeb LA
(c/o Loeb) Joseph Gottstein Memorial Cancer Res. Lab., Univ. Washington, Seattle, WA, 98195
Cancer Res; 42(9):3480-3485 1982

The effect of modifying phichi174 viral DNA by the chemical carcinogens beta-propiolactone, N-acetoxyacetylaminofluorene and anti-benzo[a]pyrene diol-epoxide was investigated by transfecting the modified DNA into Escherichia coli spheroplasts. Modification of the DNA in vitro by each of these agents was mutagenic for the phichi174 amber mutants am3 and am86. Mutagenicity depended on the induction of the 'SOS' response and the host spheroplasts. Heating beta-propiolactone-treated DNA at neutral pH caused strong inactivation such that the number of lethal hits was increased four-fold. Sucrose gradient analysis showed the induction of alkali-labile sites in the heated DNA. The 'nicked circle assay' with double-stranded phichi174 DNA showed greater than 70% of these sites to be apurinic sites. Concomitantly with the production of these new sites, a strong increase in the mutation frequency was observed. This mutagenesis also depended upon the induction of the error-prone SOS response in the spheroplasts, as was previously shown to be the case for mutagenesis at putative apurinic sites induced directly by acid-heat treatment. These results suggest that depurination may be of importance to the mechanism of mutagenesis by beta-propiolactone and other carcinogens. (Author abstract) (25 Refs)

16. THE INHALATION TOXICOLOGY OF PHENYLGLYCIDYL ETHER: REPRODUCTION, MUTAGENIC, TERATOGENIC, AND CYTOGENETIC STUDIES.

Terrill JB, Lee KP, Culik R, Kennedy GL
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Toxicol Appl Pharmacol; 64(2):204-212 1982

Inhalation toxicity of phenylglycidyl ether (PGE), at concentrations ranging from 1-12 (vol/vol) ppm and for varying periods of time, was measured in rats in a two-generation reproduction study including a dominant lethal mutagenicity assay, a teratogenicity study, and a cytogenetic evaluation of bone marrow cells. Normal fertility was observed when treated male rats were mated with untreated females, and there was no evidence of increased early embryonic death. Test progenies were delivered in normal numbers, and they survived and grew like controls. A decrease in the number of pregnancies resulting from mating during the first wk postexposure to males receiving the highest dose level (11 ppm; 19 days) suggested a treatment relationship, but all other reproductive data were apparently normal. A single pup displayed an abnormal hair pattern (curly hair), which was likely an isolated occurrence unrelated to treatment. Teratogenic studies of pregnancies of females exposed to 1, 5 and 12 ppm of PGE revealed for all levels similar levels of pregnancy at death; similar numbers of implantations, live fetuses, and resorptions; and similar characteristics of fetus size. No increases in the incidence of gaps, breaks, or rearrangements were observed in bone marrow cells from rats exposed to levels of PGE from 0-11 ppm over a 19-day period. (22 Refs)

17. LACTATIONAL INDUCTION OF HYDROXYLATION OF CARCINOGENS IN SUCKLING RATS BY INDUCERS OF CYTOCHROME P1-450 (MEETING ABSTRACT).

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Fed Proc; 41(3):1425 1982

Modification of carcinogen metabolism in suckling young (SY) through lactational transmittal of pharmacologically active compounds is of considerable interest. We have examined the effects of ip injections to lactating rats (LR) of 3-methylcholanthrene (3-MC) or beta-naphthoflavone (beta-NF) (40 mg/kg of b wt in corn oil for 3 days) on enzyme activities of hepatic microsomes (HM) of their SY. The levels of cytochromes P-450 (P1-450) and bs and activities of NADH- and NADPH-cytochrome c reductases were similar to those of HM of SY from corn oil-treated LR. The apparent induction of cytochrome P1-450 in HM of SY of 3-MC- or beta-NF-treated LR was shown by the increased hydroxylations of benzo[a]pyrene (B[a]P) and N-2-fluorenylacetamide (2-FAA). In the presence of 0.1 mM alpha-NF (alpha-naphthoflavone), the levels of hydroxylation of B[a]P or 2-FAA were similar in all 3 sets of SY and were 2.7-or 5.0-fold greater, respectively, than their basal levels. This suggests that although alpha-NF in vitro stimulates the basal hydroxylating enzyme activities, it inhibits the cytochrome P1-450-induced activities as it does in HM of LR. In the latter, alpha-NF was a more potent inhibitor than beta-NF. Binding to HM showed that beta-NF (type I) binds with a higher affinity than the type I substrates B[a]P and 2-FAA, whereas alpha-NF gives a qualitatively different binding spectrum suggestive of multiple binding sites. (no Refs)

18. EFFECTS OF FLAVONES AND ELLIPTICINE UPON SKIN TUMOR INITIATION BY ARYLHYDROCARBONS (MEETING ABSTRACT).

Alworth WL, Slaga TJ
Tulane University, New Orleans, LA, 70118
Fed Proc; 41(3):928 1982

Ten nmole 7,12-dimethylbenz[a]anthracene (DMBA), 200 nmole of dibenz[a,h]anthracene (DBA), or 47.4 nmole of 7,14-dimethyldibenz[a,h]anthracene (DDBA) were applied to Sencar mice. One week after treatment with the arylhydrocarbons (PAH), the mice began to be treated twice a week with 2 ug of 12-O-tetradecanoylphorbol-13-acetate. The production of papillomas over 21 weeks established that DDBA is a potent initiator of tumors, comparable to DMBA. Modification of tumorigenesis occurred with 7,8-benzoflavone (BF), flavone (FL), or ellipticine, 5,11-dimethyl-6H-pyrido[4-3b]carbazole, (EL) were applied 5 min prior to the PAH. BF inhibited DMBA tumorigenesis but had little effect upon DBA tumorigenesis. BF enhanced DDBA initiated tumor formation. Treatment with FL or EL stimulated DBA tumorigenesis. Applications of FL (450 nmole) or EL (2.5 nmole) also stimulated tumor formation by DMBA and DDBA, but at higher levels (4.5 umole, FL; 250 nmole, EL), these modifiers inhibited tumor initiation by DMBA and DDBA. It is concluded that the effects of FL and EL upon PAH initiated skin tumors are concentration dependent. The results indicate that two processes may be involved in the initiation of tumors by PAH, and that these processes may be distinguished by contrasting effects produced by varying levels of modifiers. (no Refs)

19. DEACETYLATION OF 4-(5-ACETYLAMINO-2-FURYL)THIAZOLE TO 1-(4-THIAZOLYL)-3-CYANO-1-PROPANONE BY RAT LIVER TISSUES (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:334 1982

We postulate metabolic reduction of the rat carcinogen 4-(5-nitro-2-furyl)thiazole (NFT) to 1-(4-thiazolyl)-3-cyano-1-propanone (TCP). This may proceed from the nitro to the amino analog through the nitroso and N-hydroxylamino intermediates. Formation of TCP could occur at the stages of either N-hydroxylamino or amino intermediates by furan ring cleavage. To examine if 4-(5-amino-2-furyl)thiazole is a precursor for TCP, a stable model compound, 4-(5-acetylamino-2-furyl)thiazole (AAFT), was synthesized and its chemical identity established by spectroscopic and mass spectral analysis. Incubation with rat liver 10,000 g supernatant preparations resulted in the biotransformation of AAFT as evidenced by a decrease in absorption at 290 nm. Incubation of 14C-labeled AAFT followed by extraction with chloroform:ether (1:1) resulted in the recovery of a major portion (56%) of the radioactivity in the organic phase when the label was at the 2-position of the thiazole ring, while the major amount (82%) of radioactivity was recovered in the aqueous phase when the 1-14C-acetyl group was labeled. The radioactivity from the aqueous phase was extractable into the organic phase following acidification to pH 1, an observation consistent with deacetylation. Furthermore, the deacetylation product exhibited a mass spectrum, and retention times in gas and high pressure liquid chromatography, similar to that of synthetic TCP. (no Refs)

20. THE THIRD CLASS OF NEW TUMOR PROMOTERS, POLYACETATES (DEBROMOAPLYSIATOXIN AND APLYSIATOXIN), CAN DIFFERENTIATE BIOLOGICAL ACTIONS RELEVANT TO TUMOR PROMOTERS.

Fujiki H, Suganuma M, Nakayasu M, Hoshino H, Moore RE, Sugimura T
Natl. Cancer Center Res. Inst., 1-1, Tsukiji 5-chome, Chuo-ku, Tokyo 104, Japan
Gan; 73(3):495-497 1982

Aplysiatoxin is a new class of potent tumor promoter and debromoaplysiatoxin may be a weak promoter. Aplysiatoxin and debromoaplysiatoxin showed the same potency on irritation of mouse ear and induction of ornithine decarboxylase activity on mouse skin, but debromoaplysiatoxin was much weaker than aplysiatoxin in induction of adhesion of HL-60 cells. (Author abstract) (12 Refs)

21. MUTAGENICITY OF NALIDIXIC ACID IN MYCOBACTERIUM PHLEI.

Konicek J, Konickova-Radochova M
Mikrobiologicky ustav, CSAV, Prague 4 - Krc, Czechoslovakia
Stud Pneumol Phtiseol Cech; 42(4):234-237 1982

The mutagenicity of nalidixic acid (1 mg/ml) in Mycobacterium phlei was studied. The substance was found to be mutagenic both in inversion induction in three different auxotrophic strains and in forward mutagenic induction of reversion, both in three different auxotrophic strains, and in forward mutation induction (auxotrophic mutation and mutation resistant to isonicotinic acid hydrazide) with a low lethal effect. (12 Refs) (In CZE)

22. MUTATION AND TRANSFORMATION IN CHINESE HAMSTER V79 CELLS AND C3H MOUSE FIBROBLAST 10T1/2 CELLS BY AFLATOXIN B1 AND FOUR OTHER FUROCOUMARINS ISOLATED FROM TWO NIGERIAN MEDICINAL PLANTS (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:370 1982

As part of the assessment of carcinogenic risk posed by furocoumarins present in the environment of Nigeria and other tropical countries, a comparative study on the mutation and transformation of four furocoumarins isolated from two Nigerian medicinal plants-Clausena anisata and Afraegle paniculata and aflatoxin B1 also a furocoumarin in Chinese hamster V79 and 10T1/2 cells have been investigated. Mutation by Aflatoxin B1 (AFB1), Imperatorin (IMP), Marmesin (MAR), Chalepin (CHAL) and Xanthotoxin or 8-methoxypsoralen (MOP) with and without long wavelength - Black light (BL) activation were monitored at hypoxanthine guanine phosphoribosyl transferase - locus (AZG R) in V79 cells and at Ouabain locus (OUA R) in 10T1/2 cells. Transformation by these furocoumarin under same activation condition in 10T1/2 cells was also investigated. AFB1 induced a 4 fold (AZG R) maximum mutation frequency over control under BL-activation at a concentration of 5 ug/ml; MAR, a maximum of 2 fold mutation frequency (AZG R) over control at 1.5 ug/ml; MOP, a maximum of 19 fold (AZG R) over control at 10 ug/ml; CHAL, a maximum of 3 fold (AZG R) over control at 5 ug/ml and IMP, a maximum of 20 fold (AZG R) over control at 10 ug/ml. In the transformation assay, types II and III foci were observed at 1 ug/ml AFB1 with or without BL-activation while in MOP and IMP these types of foci were observed under BL-activation only. MAR although relatively more cytotoxic than the other furocoumarins under investigation, with LD50 less than 0.5 ug/ml, is not as mutagenic or potentially carcinogenic as AFB, IMP or MOP under BL-activation. (no Refs)

23. ISOLATION AND STRUCTURAL DETERMINATION OF MUTAGENIC SUBSTANCES IN COAL TAR.

Kosuge T, Zenda H, Nukaya H, Terada A, Okamoto T, Shudo K, Yamaguchi K, Iitaka Y, Sugimura T, Nagao M, Wakabayashi K, Kosugi A, Saito H

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Chem Pharm Bull (Tokyo); 30(4):1535-1538 1982

Fractionation of the basic fraction of coal tar yielded 11 compounds that showed mutagenic activity in Salmonella typhimurium in the Ames test. The molecular structures of these compounds were analyzed. Six were aminopolycyclic aromatic hydrocarbons: 1-aminofluoroanthene, 1-aminophenanthrene, 3-aminophenanthrene, 1-aminopyrene, 3-aminopyrene, and 5-aminobenz[a]anthracene. Five were aza-polycyclic aromatic hydrocarbons: phenaleno[1,9-gh]quinoline, pyrido[3,2-c]carbazole, quino[3,2-c]carbazole, benzo[h]naphtho[2,1,8-def]quinoline, and benzo[de]naphtho[1,8-gh]quinoline. (7 Refs)

INORGANIC AGENTS AND PARTICULATES INCLUDING FIBERS

24. FACTORS WHICH MODULATE PHAGOCYTOSIS OF POTENTIALLY CARCINOGENIC NICKEL SULFIDE PARTICLES (MEETING ABSTRACT).

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Fed Proc; 41(3):1225 1982

Amorphous nickel sulfide (NiS) is a water-insoluble particulate compound which is noncarcinogenic in vivo and which lacks morphological transforming activity in cultured Syrian hamster embryo (SHE) cells, while NiS having a crystalline structure is potently carcinogenic and induces SHE cell transformation in vitro. The selective phagocytic uptake of the crystalline NiS particles is hypothesized to be the determinant of their toxicological potency and appears to be related to their overall negative surface charge. Phagocytic uptake of positively charged amorphous NiS particles was induced by alteration of their surface charge with LiAlH4 reduction, this was also associated with an increased incidence of morphological transformation. Phagocytic uptake of crystalline, but not amorphous NiS particles occurs in a variety of cell types and is not dependent upon the presence of serum or protein constituents of the cell growth medium. Phagocytosis of crystalline alpha NiS particles occurs readily in a simple salts/glucose medium consisting of 50 mM Hepes Buffer pH 7.2, 100 mM NaCl, 5 mM KCl2, 5 mM glucose and 2 mM CaCl2. Reduction in Ca++ concentration resulted in a decrease in phagocytosis of crystalline alpha NiS particles. Additional studies suggest that the particle uptake by these facultative phagocytes has an absolute requirement for Ca++. (no Refs)

25. REDUCTION OF PULMONARY ADENOMAS IN STRAIN A/J MICE AFTER INTRATRACHEAL INSTILLATION OF NICKEL SUBSULFIDE (MEETING ABSTRACT).

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Ballelle Columbus Laboratories, Columbus, OH, 43201

Proc Am Assoc Cancer Res; 23:200 1982

We compared the incidence of pulmonary adenomas in strain A/J mice administered particles of nickel subsulfide by both intratracheal (IT) and intraperitoneal (IP) routes. Based on an intratracheal range finding toxicity study, the following 15-week intratracheal and intraperitoneal dosage regimens were utilized: 0.160 mg/kg or 0.053 mg/kg administered once per week or once every 3 weeks. Urethane was administered by both routes as a positive control and both untreated and vehicle control groups were incorporated into the experiment. Twenty weeks after the first dose, mice were sacrificed and pulmonary adenomas counted with a dissecting microscope. Urethane given by intratracheal and intraperitoneal routes induced 0.9 and 0.8 tumors/mouse, respectively. Combined untreated and vehicle control mice for each of the exposure routes had 0.15 tumors/mouse. There was no significant difference in the numbers of pulmonary adenomas per mouse between combined controls and any dose group or combination of dose groups injected intraperitoneally with nickel subsulfide. However, when adenoma incidence in pooled controls was compared to that in pooled high dose intratracheally intubated animals, significantly fewer tumors were seen in nickel-treated animals. The same trend was exhibited by the lower intratracheally administrered dose group which had less adenomas than controls. (no Refs)

26. NICKEL DISTRIBUTION AND DNA LESIONS INDUCED IN RAT TISSUES BY THE CARCINOGEN NICKEL CARBONATE.

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Cancer Res; 42(9):3544-3549 1982

DNA lesions in nuclei isolated from rat tissues following ip injection of the carcinogen nickel carbonate were measured by the alkaline elution technique. Kidney, liver, lung, and thymus gland nuclei were examined at 3 and 20 hr after treatment for the presence of DNA single-strand breaks and cross-links. Single-strand breaks were detectable in lung and kidney nuclei, and both DNA-protein and DNAS interstrand cross-links were detectable in kidney nuclei. No DNA damage was observed in liver or thymus gland nuclei. A dose response to both single-strand breaks and cross-links was observed in kidney nuclei. Time course studies revealed that maximum DNA damage in kidney nuclei occurred at 2 to 4 hr following injection and also revealed the presence of an active repair process in these nuclei. Repair-resistant DNA-protein cross-links were observed to persist through 48 hr. Tissue and intracellular nickel concentrations as measured by electrothermal atomic absorption spectroscopy were observed to correlate with the levels of DNA damage and repair. A dose response to the concentration of nickel in tissues and nuclei was observed. These results are discussed relative to the solubilization, toxicity, and carcinogenicity of nickel compounds. (Author abstract) (45 Refs)

27. INDUCTION OF ORNITHINE DECARBOXYLASE IN HAMSTER TRACHEAL EPITHELIAL CELLS EXPOSED TO ASBESTOS AND 12-O-TETRADECANOYLPHORBOL-13-ACETATE.

Landesman JM, Mossman BT
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Cancer Res; 42(9):3669-3675 1982

Crocidolite asbestos and chrysotile asbestos and the tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA), induce ornithine decarboxylase (ODC) in hamster tracheal epithelial cells (HTE-B). When added at the time cells were plated, nongrowth-inhibitory amounts of crocidolite (0.64 to 1.28 ug/sq cm) and chrysotile (0.064 to 0.13 ug/sq cm) asbestos increased ODC activity two- to three-fold after 24 to 30 hr. The effect was dose dependent. The nonfibrous mineral hematite (0.64 to 1.28 ug/sq cm) had no effect. Asbestos-stimulated induction did not occur in confluent monolayers unless fresh medium was added simultaneously. Under these conditions, both crocidolite (3-fold increase) and chrysotile (4-fold increase) induced ODC. TPA (0.1 ug/ml medium) produced a rapid transient increase in ODC activity in both logarithmically growing (6-fold increase) and confluent (30-fold increase) HTE-B. When TPA and fresh medium were combined, a synergistic effect was noted both in 24-hr cultures (22-fold increase) and at confluency (72-to 92-hr cultures; 170-fold increase). The addition of asbestos and TPA alone had no effect on [3H]thymidine incorporation in confluent monolayers; however, a significant mitogenic response was observed when they were added with fresh medium. Under these circumstances, the cells appeared morphologically transformed. The ability of asbestos to induce ODC and influence proliferation of HTE-B is consistent with the results of previous observations in our laboratory. These studies indicate that asbestos is producing a constellation of changes warranting its classification as a tumor promoter in the respiratory tract. (Author abstract) (44 Refs)

28. IMMUNOTOXICOLOGY STUDIES ON LEAD: EFFECTS OF EXPOSURE ON TUMOR GROWTH AND CELL-MEDIATED TUMOR IMMUNITY AFTER SYNGENEIC OR ALLOGENEIC STIMULATION.

Kerkvliet NI, Baecher-Steppan L
Sch. Veterinary Medicine, Oregon State Univ., Corvallis, OR, 97331
Immunopharmacology; 4(3):213-224 1982

Chronic exposure of C57Bl/6 mice to lead acetate in drinking water enhanced growth of primary Maloney sarcoma virus (MSV)-induced tumors. In a subsequent continued survival study, exposed mice showed a decrease in late-appearing progressive tumors. Cell-mediated cytotoxic response in spleen or lymph nodes of tumor-bearing mice was significantly augmented by lead exposure. Further studies in an allogeneic tumor model and studies of macrophages from lead-exposed mice suggest significant impairment of macrophage function by lead. (33 Refs)

29. THE ULTRASTRUCTURAL LOCALIZATION OF BERYLLIUM IN BIOLOGICAL SAMPLES BY ELECTRON ENERGY-LOSS SPECTROMETRY.

Dinsdale D, Bourdillon AJ
MRC Toxicology Unit, Medical Res. Council Lab., Woodmansterne Road, Carshalton, Surrey SM5 4EF, England
Exp Mol Pathol; 36(3):396-402 1982

The toxic, carcinogenic element beryllium has been localized in biological tissues at the ultrastructural level. A suspension of beryllium phosphate particles, the predominant form in which beryllium is transported in the bloodstream, was administered intravenously to rats. This form of beryllium is known to be accumulated, almost exclusively, by the Kupffer cells of the liver. The liver from each rat was prepared for electron microscopy and analyzed by electron energy-loss spectrometry. Beryllium was not detected in the nuclei or cytoplasm of any liver cells but its presence (ca 1 x 10(-18) g), together with phosphorus and oxygen, was demonstrated in particles within the secondary lysosomes of Kupffer cells. (Author abstract) (15 Refs)

30. THE INFLUENCE OF ASBESTOS ON THE FORMATION AND REMOVAL OF BENZO(A)PYRENE-DNA ADDUCTS IN A HAMSTER TRACHEAL EPITHELIAL CELL LINE (MEETING ABSTRACT).

Eastman A, Mossman BT, Bresnick E
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Proc Am Assoc Cancer Res; 23:236 1982

The effect of asbestos fibers (crocidolite and chrysotile) on the interaction of benzo(a)pyrene (BP) with a hamster tracheal epithelial cell line (HTE-B) has been investigated. When BP alone was incubated with HTE-B cells, 50% of the applied hydrocarbon was recovered as water soluble metabolites at 8 hr while 5% was recovered as intracellular unmetabolized BP. After 8 hr incubation with BP, the medium was replaced and a 50% reduction in alkylation was observed in 24 hr with about 80% removed by 5 days. High performance liquid chromatography separation of the DNA adducts demonstrated six adducts. Of these six adducts, two were rapidly removed while two were relatively poorly removed during the 5 day repair period. In comparative studies, BP was coated onto asbestos and applied to HTE-B cells. An enhanced uptake was observed with 80% BP associated with the cells after 1 hr. Metabolism was only slightly inhibited as compared to experiments without asbestos but at 8 hr nearly 50% of the applied hydrocarbon was retained by the cells in unmetabolized form. Analysis of repair was complicated by continued formation of alkylated products in DNA after removal of BP. However, after 24 hr post-treatment, only 5% of the applied BP remained in the cells. At 5 days, it appeared that removal of DNA-bound adducts was inhibited. Experiments with both crocidolite and chrysotile gave the same results. It is concluded that the cocarcinogenic effect of asbestos may be due to enhanced cellular uptake of BP as well as inhibition of subsequent DNA repair. (no Refs)

31. A PROBABLE MECHANISM FOR SYNERGISTIC EFFECT IN CHRYSOTILE AND BAP INDUCED TRANSFORMATION (MEETING ABSTRACT).

Chang MJ, Singh NP, Hart RW
National Center for Toxicological Research, Jefferson, AR, 72079
Proc Am Assoc Cancer Res; 23:199 1982

It is generally believed that the initial step of chemically induced cellular transformation is the fixation of DNA damage(s). Using a normal human skin fibroblast cell culture system, we investigated: 1) the cytotoxic effect of chrysotile asbestos; 2) thymidine incorporation, and 3) cellular uptake of BaP (benzo(a)pyrene) under the influence of asbestos. We observed: 1) chrysotile asbestos (10 ug/ml) exerted cytotoxicity at a cell density below confluency; 2) chrysotile treatment enhanced thymidine incorporation from the first to the fourth day post-treatment both in the presence or absence of BaP; 3)

BaP uptake was enhanced in the culture simultaneously treated with asbestos. The preliminary findings indicate that protein and RNA binding of BaP was enhanced in the presence of chrysotile asbestos. Based on the data collected, we suggest that in the event of co-exposure of chrysotile asbestos and BaP, more DNA damage will result, that thymidine incorporation will be enhanced and is indicative of increased levels of DNA replication thereby leading to the fixation of genetic damage. (no Refs)

32. ENVIRONMENTAL FIBER-INDUCED PLEURO-PULMONARY DISEASES IN AN ANATOLIAN VILLAGE: AN EPIDEMIOLOGIC STUDY.

Artvinli M, Baris YI
Dept. Chest Diseases, Sch. Medicine, Hacettepe Univ., Ankara, Turkey
Arch Environ Health; 37(3):177-181 1982

This study was designed to determine the prevalence of pleural mesothelioma and other malignancies in the Anatolian village of Tuzkoy, where neither asbestos nor any environmental carcinogen has been detected. Another village (Kizilkoy) located 12 km from Tuzkoy was selected as a control. Three hundred twelve subjects from Tuzkoy who were at least 25 yr of age and 95 subjects from Kizilkoy were studied. Analysis of x-rays of the Tuzkoy group revealed that subjects had calcified pleural plaques (17%), pleural thickening (10.5%), obscured costophrenic angles (15%), and diffuse interstitial pulmonary fibrosis (12.1%). Sixty-seven deaths were recorded in Tuzkoy during the previous 3 yr, 41 of which resulted from malignant diseases. There were no x-ray abnormalities or deaths resulting from malignancies in the control group. Because of the high incidence of mesothelioma and lung cancer which usually results from asbestos exposure, the presence of asbestos in Tuzkoy was investigated, but none was detected in spite of Tuzkoy's volcanic location. Nevertheless, zeolite, an asbestiform mineral, was detected in the stones of buildings and in the village soil, as well as in the lung and pleura of the patients during biopsy. Thus, this mineral was considered to be responsible for the fiber-induced pleuro-pulmonary diseases in Tuzkoy. No zeolite was found in the soil and stones of the control village. (Author abstract) (17 Refs)

33. FIRST EXPERIMENTAL DEMONSTRATION OF THE ONCOGENIC EFFECTS OF A ZEOLITE ON THE PLEURA. PRODUCTION OF MESOTHELIOMA IN SPRAGUE-DAWLEY RATS BY ERIONITE.

Maltoni C, Minardi F, Morisi L
Inst. Oncology, Bologna, Italy
Acta Oncol (Padova); 2(1/2):137-140 1981

Effects of asbestos and industrial zeolites, including erionite, were tested by ip or intrapelural injection in 20 male and 20 female 4-wk-old Sprague-Dawley rats. Each compound was injected in one standard dose of 25 mg in 1 ml H2O. Two males died after 32 and 40 wk, and one female after 47 wk. A pleural mesothelioma was observed in the male rat that died after 32 wk. Among 40 animals treated with crocidolite, no pleural mesotheliomas were observed after 50 wk. (1 Ref)

34. OVARIAN CANCER AND TALC. A CASE-CONTROL STUDY.

Cramer DW, Welch WR, Scully RE, Wojciechowski CA
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Cancer; 50(2):372-376 1982

Opportunities for genital exposure to talc were assessed in 215 white females with epithelial ovarian cancers and in 215 control women from the general population matched by age, race, and residence. Ninety-two (42.8%) cases regularly used talc either as a dusting powder on the perineum or on sanitary napkins compared with 61 (28.4%) controls. Adjusted for parity and menopausal status, this difference yielded a relative risk of 1.92 (p less than 0.003) for ovarian cancer associated with these practices. Women who had regularly engaged in both practices had an adjusted relative risk of 3.28 (p less than 0.001) compared to women with neither exposure. This provides some support for an association between talc and ovarian cancer hypothesized because of the similarity of ovarian cancer to mesotheliomas and the chemical relation of talc to asbestos, a known cause of mesotheliomas. The authors also investigated opportunities for potential talc exposure from rubber products such as condoms or diaphragms or from pelvic surgery. No significant differences were noted between cases and controls in these exposures, although the intensity of talc exposure from these sources was likely affected by variables not assessed in this study. (Author abstract) (24 Refs)

35. FLAME-ATTENUATED FIBERGLASS: ANOTHER ASBESTOS?

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Am J Industr Med; 3(1):121-125 1982

The possibility that flame attenuation produced fiberglass is a health hazard to workers exposed for long periods is addressed. Animal studies have demonstrated that fine or thin fiberglass with lengths greater than 8 microns has an effect similar to that of asbestos in producing pleural sarcoma. While epidemiologic studies have demonstrated site-specific increases in mortality, problems with these studies make conclusions impossible. Five types of studies are suggested for the decade 1980-1990 to determine the actual health hazards of long-term exposure. (12 Refs)

AMIDES, CARBAMATES AND UREAS

36. MAMMARY TUMOR INDUCTION IN INBRED MOUSE STRAINS WITH URETHANE IS NOT ACCOMPANIED BY CHANGES IN EXPRESSION OF B- AND C-TYPE RETROVIRAL STRUCTURAL PROTEINS.

Imai S, Morimoto J, Tsubura Y, Hilgers J
Dept. Pathology, Nara Medical Coll., 840 Shijo-cho, Kashihara-shi, Nara-ken 634, Japan
Int J Cancer; 30(1):101-106 1982

Urethane administered in the drinking water of breeding female mice of five inbred strains (DDf, KF, C3Hf, ddY and C57BL) leads to a higher incidence of mammary tumors at an extremely early age in four of these strains (DDf, KF, C3Hf and ddY). In the case of the DDf strain the tumors are adenoacanthomas, but in the case of the other strains adenocarcinomas are also observed. The effect of urethane in the drinking water on expression of endogenous retroviral structural proteins of the B and C type (MTV and MuLV) was studied in the milk by an immunodiffusion test and in organ extracts by radioimmunoassays (for MTVp27, MTVgp52 and MuLVp30). Organs tested include salivary glands, thymus and spleen from female and male animals. In addition, prostate and seminal vesicles were tested in male animals and uterus and mammary glands in females. Mammary tumors induced by urethane were also tested. Urethane does not induce or enhance endogenous retroviral antigen expression, either in these organs or in the mammary gland, one of the target organs for tumorigenesis by this agent. (Author abstract) (34 Refs)

37. TRANSPLACENTAL EFFECTS OF CARCINOGENIC AND NONCARCINOGENIC SUBSTANCES ON THE PYRUVATE KINASE (PK) AND LACTATE DEHYDROGENASE (LDH) ACTIVITIES OF THE MOUSE LUNG AND ON THE LDH ISOENZYME SPECTRUM.

Rady P, Arany I, Uzvolgyi E, Bojan F, Kertai P

Kozegeszsegtani es Jarvanytani Intezet, Debreceni Orvostudomanyi Egyetem, Debrecen, Hungary

Magy Onkol; 26(2):153-161 1982

The effects of carcinogenic and noncarcinogenic substances, administered ip on day 18 of pregnancy, on the PK and LDH activities and on the H/M isoenzyme ratio of LDH in the lungs were studied in the offspring of CFLP mice on day 19 of intrauterine life and on days 1-35 of extrauterine life, ie, before the manifestation of lung tumors. The substances administered included the carcinogens urethane (UR: 1,000 mg/kg), 3-methyl-cholanthrene (MC: 10 mg/kg) and dimethylnitrosamine (DMN: 10 mg/kg); noncarcinogenic analogs of carcinogens: phenylurethane (PHU: 100 mg/kg) and pyrene (20 mg/kg), and paraquat (PAR: 20 mg/kg), a noncarcinogenic substance toxic for the lungs. UR, MC and DMN were found to increase the PK and LDH activities in the lungs already on day 19 of intrauterine life. The enzyme activities showed further increases during the first days of extrauterine life to decline beginning from day 7 of life, but still being significantly increased on day 35. Unlike the noncarcinogenic analogs, PAR was found to cause a transient increase in the PK and LDH activities during the intrauterine and extrauterine lives. The H/M isoenzyme ratio of LDH was reduced by UR, and the reduction was still significant on day 35. The H/M ratio was transiently reduced by PAR, while PHU, the only noncarcinogenic analog tested in this respect, caused no change in the isoenzyme ratio. (28 Refs) (In HUN)

38. IN VITRO ACTIVITY OF ARYL HYDROXYLASES IN THE LIVER UNDER THE EFFECTS OF VARIOUS SUBSTANCES.

Fonberg-Broczek M, Urbanek-Karlowska B, Czerwiecki L

Zaklad Badania Zywnosci i Przedmiotow Uzytku, Panstwowy Zaklad Higieny, ul. Chocimska 24, 00-791 Warsaw, Poland

Rocz Panstw Zakl Hig; 32(5/6):427-431 1981

The effects of various substances on the activity of aryl hydroxylases which play an important role in the metabolic activation of carcinogenic substances (diphenyl 2-hydroxylase and diphenyl 4-hydroxylase) in mouse liver were studied in vitro. Both hydroxylases were activated by aflatoxin B1 and allyl isopropylacetamide. The activity of diphenyl 2-hydroxylase was raised selectively by piperonyl butoxide. (10 Refs) (In POL)

39. ENHANCEMENT OF ULTRAVIOLET-INDUCED UNSCHEDULED DNA SYNTHESIS IN HELA CELL LYSATE BY APHIDICOLIN IN VIVO.

Hanaoka F, Yamada K, Kato H, Yamada M

Dept. Physiological Chemistry, Faculty Pharmaceutical Sciences, Univ. Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Biochem Biophys Res Commun; 107(1):1-5 1982

The effect of DNA synthesis inhibitors on UV-induced unscheduled DNA synthesis in HeLa cells and in cell-free homogenates was investigated. Aphidicolin inhibited unscheduled DNA synthesis (UDS) at UV damaged sites in cellular DNA. This inhibition was reversible in cell free homogenates fortified with sufficient deoxynucleotide-triphosphates. A linear and parallel correlation was observed between UDS in intact cells and incorporation of tritiated deoxythymidine triphosphate in homogenates. Combined treatment with aphidicolin and hydroxyurea induced higher UDS in cell-free homogenates than did aphidicolin alone. 2',3'-Dideoxythymidine and arabinofuranoysl cytosine had little effect on UDS. (17 Refs)

AMINO ACID ANALOGS AND MODIFIED NUCLEIC ACID CONSTITUENTS

40. ACTIVATION OF TRP-P-1 AND TRP-P-2 IN VITRO AND IN VIVO.

Dolara P, Caderni G, Benetti D

Inst. Pharmacology and Toxicology, Univ. Florence, Florence, Italy

Nutr Cancer; 3(3):168-171 1982

Isolated perfused livers were not able to activate the promutagens Trp-P-1 and Trp-P-2 to their genotoxic metabolites. On the contrary, inherently active mutagenic compounds were detected in the bile of living rats to which Trp-P-1 and Trp-P-2 had been administered intravenously. The excretion of active mutagens through the bile may explain the tumorigenic effect that these compounds exert on the liver during chronic feeding experiments. (Author abstract) (8 Refs)

41. EFFECT OF PYRIDOXAL DEFICIENCY ON PANCREATIC DNA DAMAGE AND NODULE INDUCTION BY AZASERINE (MEETING ABSTRACT).

Zurlo J, Roebuck BD, Rutkowski JV, Curphey TJ, Longnecker DS

Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, NH, 03755

Proc Am Assoc Cancer Res; 23:264 1982

The purpose of this study was to determine whether the effects of azaserine on pancreas are pyridoxal-dependent. For DNA damage studies, weanling rats were fed a pyridoxal deficient diet containing 4-deoxypyridoxine, a pyridoxal antagonist, until deficiency was evident (10-12 days). They were then injected with azaserine 90 min before sacrifice. The deficient rats inhibited almost no pancreatic DNA damage (as determined by alkaline elution) in response to azaserine when compared to saline-treated rats on control diet. A structurally different pancreatic carcinogen, Ndelta-(N-methyl-N-nitrosocarbamoyl)-L-ornithine, caused DNA damage in both deficient and control groups. Distribution studies with 14C-azaserine showed that the absence of DNA damage was not due to the lack of azaserine transport into the pancreases of deficient animals. In another study, rats were treated with 4-deoxypyridoxine prior to a single azaserine treatment. Rats were killed 4 mo after azaserine administration. There was a significant reduction in the number of atypical acinar cell nodules in antagonist-treated animals compared to controls treated with azaserine but not with the antagonist. These results strongly indicate that azaserine metabolism and carcinogenicity are dependent on pyridoxal. (no Refs)

42. STUDIES ON THE BIOLOGIC ACTIVITY OF PURINE AND PYRIMIDINE ANALOGS.

Montgomery JA
Southern Res. Inst., Birmingham, AL, 35255
Med Res Rev; 2(3):271-308 1982

Biologic activity of purine-pyrimidine antimetabolites including 6-thiopurines, azapurine, alpha-arabinonucleotides, carbolic analogs of nucleosides, purines and pyrimidines containing chemically reactive functions, deazapurines, and halopurines is reviewed. Among 9-substituted purines, 9-amino-6-mercaptopurine and some of its derivatives showed activity in the L1210 system comparable to 6-mercaptopurine (MP) and may owe their activity to in vivo conversion to MP. The responses of resistant cell lines indicated that the cytotoxicity of 2-azaadenosine is due both to its direct phosphorylation and to its conversion to 2-azahypoxanthine which is known to inhibit the growth of both microbial and mammalian cells. Carbocyclic analogs of nucleosides have a carbon-nitrogen bond joining the heterocyclic base to the cyclopentane ring comparable to that of simple alkyl derivative and, therefore, not susceptible to enzymatic fission as is the glycosyl bond of true nucleosides. The activity of the monofunctional alkylating agent N-(2,4-dinitrophenyl)aziridine provided the basis for the synthesis of some 6-(1-aziridinyl)purines, which showed activity against adenocarcinoma 755, a tumor not normally sensitive to alkylating agents. The activity of N-methyl-N-nitrosourea suggested the incorporation of this moiety into a purine structure. The cytotoxicity of 3-deoxyadenosine is enhanced by 2'-deoxycoformycin, which is less effective with 9-beta-D-xylofuranosyladenine, even though both compounds are deaminated by adenosine deaminase at a significant rate. (175 Refs)

ALIPHATIC HALOGEN COMPOUNDS

43. TOXICOLOGY OF 1,1-DICHLOROETHANE.

Elskamp DM
Medical Biological Lab. RVO-TNO, Rijswijk, The Netherlands
Toxicology of 1,1-dichloroethane. Available from National Technical Information Service, Springfield, VA, as PB82-182809:, 14 pp., 1981.

The report gives the results of a search of the literature for the toxic characteristics of 1,1 dichloroethane. Subsequently is dealth with technical data, environmental and biological monitoring, toxicokinetics and data of acute and chronic toxicity for laboratory animals and humans. Also the effects of reproduction and mutagenic and carcinogenic effects are discussed. (Author abstract) (In DUT)

44. HISTOPATHOLOGY AND CELL-MEDIATED IMMUNE REACTIVITY IN HALOTHANE-ASSOCIATED LYMPHOMAGENESIS AND AUTOIMMUNITY IN BXSB/MP AND MRL/MP MICE.

Lewis RE, Cruse JM, Johnson WW, Mohammad A
Dept. Pathology, Univ. Mississippi Medical Center, 2500 North State St., Jackson, MS, 39216
Exp Mol Pathol; 36(3):378-395 1982

The present study examined whether halothane anesthesia could alter immunoregulation in autoimmune disease-prone BXSB/Mp and MRL/Mp mice. This was judged by histopathological examination of lymph nodes and by studies on mitogen-induced transformation of splenic lymphocytes. The development of lymphoma-like disease in BXSB males and the appearance of lymphoproliferation and systemic lupus erythematosus-like disease in MRL/Mp lpr/lpr mice were revealed by histologic examination of lymph nodes and other tissues and by identification of immune complexes in kidney sections by immunofluorescence. Splenic lymphocytes from MRL/Mp +/+ mice exposed to halothane showed a 44% reduction in mean stimulation indices (MSI) compared to exposure to O2. Likewise, the MSI of splenic lymphocytes from MRL/Mp lpr/lpr mice exposed to halothane were reduced to 42% when compared with those from MRL/Mp lpr/lpr mice subjected to O2. In accord with the MRL results, halothane induced a 38% reduction in the stimulation indices of autoimmune and lymphoma-like disease-prone BXSB mice and a 27% decline in the lymphocyte proliferative responsiveness of autoimmune disease-insusceptible control C57Bl/6 mouse spleen cells, compared to their respective O2 control values. Results demonstrate that halothane facilitated an earlier onset in loss of immunoregulation associated with development of autoimmunity and lymphomagenesis in genetically disease-prone mice receiving halothane than in those receiving oxygen. (Author abstract) (13 Refs)

45. DETECTION OF DNA INTERACTION WITH BIS(CHLOROMETHYL)ETHER AND FORMALDEHYDE IN EPITHELIAL CELLS BY USE OF S-1 NUCLEASE (MEETING ABSTRACT).

Belman S, Garte SJ
Department of Environmental Medicine, New York University Medical Center, New York, NY, 10016
Proc Am Assoc Cancer Res; 23:251 1982

Bis(chloromethyl)ether (BCME) and HCHO (formaldehyde) are carcinogens for the respiratory tissues of rats. BCME can be formed from HCHO + HCl. We are studying the interactions of these agents with DNA by measuring DNA damage with the S-1 nuclease assay. BCME produced dose-related DNA damage up to 320 uM, which was not affected by the presence of dideoxythymidine (10 ug/ml). This indicates that rapid repair of DNA breaks did not occur under these conditions. The max amount of damage was not altered at the increased dose of 640 uM. Exposure to BCME for 15, 30, and 45 min produced the same amount of damage at all doses. This is expected from the short half life of BCME aqueous solutions. Formaldehyde produced no DNA damage but appears to have prevented the alkaline unwinding of control DNA. This was observed at doses of 300-2560 uM. The DNA damage produced by 1 hr incubation with 8 uM 4-NQO (4-nitroquinoline-1-oxide) was decreased in the presence of HCHO. A dose-related decrease in 4-NQO-induced damage was observed from 300 uM HCHO. This effect of HCHO can be interpreted as a consequence of its known ability to produce crosslinks in DNA and protein, which would prevent alkaline unwinding of DNA. (no Refs)

46. VINYLIDENE CHLORIDE: ITS METABOLISM BY HEPATIC MICROSOMAL CYTOCHROME P-450 IN VITRO.

Costa AK, Ivanetich KM

(c/o Ivanetich) Dept. Medical Biochemistry, Univ. Cape Town Medical Sch., Observatory, C.P. 7925, South Africa

Biochem Pharmacol; 31(11):2083-2092 1982

The effects of inducing agents on the binding and metabolism of vinylidene chloride by hepatic microsomal cytochrome P-450 are reported. Hanes plots for the Type I binding of vinylidene chloride to cytochrome P-450 were biphasic with hepatic microsomes from untreated and beta-naphthoflavone or phenobarbital-treated male rats. Neither pretreatment affected the value of the Ks for the high-affinity binding site for vinylidene chloride, while phenobarbital induction, but not beta-naphthoflavone treatment, decreased the value of the Ks for the low-affinity site by three-fold. It is concluded that multiple forms of cytochrome P-450 bind and metabolize vinylidene chloride. However, the form of the enzyme elevated by phenobarbital plays, at most, a minor role in these processes, while the form induced by beta-naphthoflavone is not involved in either process. The effect of metabolism of vinylidene chloride by cytochrome P-450 on the relationship between the metabolism and toxicity of vinylidene chloride in vivo and its mutagenicity in vitro is considered. (37 Refs)

47. INDUCTION OF HEPATOCELLULAR NUCLEOSIDE-5'-TRIPHOSPHATASE (ATPASE) DEFICIENT FOCI BY VINYL CHLORIDE (VC) (MEETING ABSTRACT).

Laib RJ, Bolt HM

International Agency for Research on Cancer, 69372 Lyon Cedex 2, France

Proc Am Assoc Cancer Res; 23:231 1982

In many species including man, VC induces angiosarcomas originating from endothelial cells of the liver, while in newborn rats, hepatocytes are more susceptible. This effect can be quantified by evaluating preneoplastic hepatocellular foci with ATPase deficiency. Rats were exposed to 2000ppm VC (8hrs/day), either transplacentally (schedule A) or immediately after birth for different time intervals (B-E), and from the age of 21 days onwards (F). Four-month old animals were sacrificed and the livers evaluated histochemically for ATPase deficient foci. Transplacental exposure (A) and schedule B revealed no increase in ATPase deficient foci, possibly due to the low rate of VC metabolism at this developmental stage. The % foci increased from schedule C to D but was not further enhanced after prolonged exposure (E). Only a few ATPase deficient foci were observed when exposure started 21 days after birth (F). As shown previously, a 70 day exposure of adult female rats to VC also did not result in ATPase deficient foci. These results indicate that the initiation of preneoplastic lesions of VC in rat hepatocytes is restricted to the early lifetime and that VC does not exert a substantial growth-promoting effect on induced ATPase deficient foci. (1 Ref)

48. HEPATOTOXIC AND CANCEROUS ACTIVATION OF GAMMA-GLUTAMYLTRANSFERASE IN RAT LIVER (MEETING ABSTRACT).

Fiala S, Payne RR, Trout EC, Kettering WG, Fiala A
Cell Physiology Laboratory, Veterans Administration Medical Center, Martinsburg, WV, 25401
Med Pediatr Oncol; 10(1):103 1982

Hepatotoxic compounds benzyl chloride, gamma-hexachlorocyclohexane, carbon tetrachloride, and the pesticide Kerb, and carcinogenic 3'-Me-DAB, administered to Sprague-Dawley male rats in one or two large doses, produced in 24 hrs a striking increase in the liver of the activity of gamma-glutamyl transferase (GGT) and a definite increase of total DNA. An increase in the number of GGT (+) hepatocytes was detected histochemically. In contrast to the induction by 3'-Me-DAB of simultaneous increases of GGT and of the glutathione (GSH) concentration during the period of 24-48 hrs, the increase of GGT produced by hepatotoxic compounds was accompanied by a decrease of GSH which forced GGT to return in 48 hrs to initial values. In hypophysectomized rats hepatotoxic compounds and 3'Me-DAB produced an increase of GGT which rapidly fell to the initial level without any substantial change in the concentration of GSH. From these experiments we concluded that: 1) Increase of GGT alone is not a specific effect of hepatocarcinogens in rat liver, but can be produced by various compounds which are toxic to liver tissue; 2) Not GGT alone, but only the combination of GGT with GSH is the Marker of rat liver carcinogenesis; 3) 3'-Me-DAB inactivates the feedback which keeps the levels of GSH and of GGT constant at the normal values; 4) Hepatotoxic compounds, as long as they do not damage the GSH-GGT feedback, are not carcinogenic for rat liver; 5) In hypophysectomized rats 3'-Me-DAB does not produce tumors because in their livers it is only hepatotoxic and does not become carcinogenic. A model will be proposed of GSH-GGT feedback, its nature, and function. Hepatotoxic effect of a compound has a relatively low affinity for vital receptors and can easily be removed, so that they are not permanently changed. The cancerous effect concerns receptors not essential to the life of the cell and involved in the social rather than the vital functions. The affinity for their receptors is high. (no Refs)

POLYHALOGENATED RING COMPOUNDS INCLUDING INSECTICIDES

49. THE GAMMA-GLUTAMYL TRANSPEPTIDASE (GGT) ACTIVITY OF LIVER LESIONS IN RATS EXPOSED TO AROCLOR 1260 (MEETING ABSTRACT).

Cihla HP, Weltman RH, Pitot HC, Norback DH
William S. Middleton Memorial Veteran's Administration Hospital,, University of Wisconsin Madison, WI, 53705
Toxicologist; 2(1):97 1982

The livers of Sprague-Dawley rats chronically fed Aroclor 1260 (100 ppm for 16 months followed by 50 ppm for 8 months) sequentially developed areas of hepatocellular alteration, neoplastic nodules, and hepatocellular carcinomas. Lesions of ductal morphology consisted of simple and cystic cholangiomas, cholangiofibrosis, and the ductal element of mixed hepatocholangiocellular carcinoma (MHC). Pure cholangiocellular carcinoma was not found. Pathologic lesions were histologically and histochemically assessed. While normal hepatocytes were GGT negative, the earliest hepatocellular lesion demonstrated homogeneous GGT activity and the later lesions were progressively more heterogeneous. Normal bile duct epithelial cells and the epithelia of both simple and cystic cholangiomas were uniformly and intensely GGT positive. The epithelium of cholangiofibrosis was GGT negative, although entrapped areas of neoplastic hepatocytes were GGT positive. The ductal element of MHC was GGT positive. Stromal elements associated with cholangiofibrosis and MHC were GGT negative. Lesions of connective tissue origin, such as fatty infiltration and early fibrosis, and a hepatocellular carcinoma with extreme fatty degeneration with infiltration were GGT negative. (no Refs)

50. DRUG METABOLIZING ENZYMES IN THE LIVERS AND HEPATIC TUMORS OF RATS TREATED WITH POLYCHLORINATED BIPHENYLS (MEETING ABSTRACT).

Reddy G, Cihla HP, Weltman RH, Norback DH
William S. Middleton Memorial Veterans Administration Hospital,, University of Wisconsin Madison, WI, 53705
Toxicologist; 2(1):64 1982

Hepatic drug metabolizing enzyme activities in the livers of rats were investigated after chronic exposure to Aroclor 1260 (PCB) or 2,3,6,2',3',6'-hexachlorobiphenyl (HCB). Sprague-Dawley rats of both sexes were fed diets containing PCB (100 ppm for 16 mo followed by 50 ppm) or HCB (100 ppm for 9 mo followed by 5 mo period of intermittent exposure followed by 100 ppm). After 24 mo they were fed a normal diet until sacrifice. The hepatic microsomal enzyme activities of aldrin epoxidase (AE), styrene oxide epoxide hydrolase (EH), and cytosolic glutathione S-epoxide transferase (GT) and the quantity of cytochrome P-450 were measured. Livers from male rats fed HCB contained enzyme levels equal to or decreased from that of controls. Livers from PCB fed male rats showed enzyme levels 1.3 to 4 fold higher than that of controls. Livers from female rats exposed to HCB showed enzyme levels equal to or decreased from control levels. Liver tumors or surrounding tissues of female rats fed PCB showed 2 to 10 fold higher enzyme activities and cytochrome P-450 content than controls. AE activity was slightly higher in surrounding tissues than in tumor, while EH activity was 1.5 times higher in the tumors than in the surrounding tissues. The levels of P-450 and GT in tumors and in surrounding tissue were nearly equal. In conclusion, increased enzyme activities and P-450 content persisted 2 to 5 months after discontinuation of PCB exposure. (no Refs)

51. ASSESSMENT OF THE CAPACITY OF POLYBROMINATED BIPHENYLS TO SERVE AS PROMOTERS OF HEPATOCARCINOGENESIS (MEETING ABSTRACT).

Jensen RK, Sleight SD, Goodman JI, Aust SD, Trosko JE
Department of Pathology, Michigan State University, East Lansing, MI, 48824
Toxicologist; 2(1):99 1982

Large doses of Firemaster (FM), a mixture of polybrominated biphenyls (PBB), cause hepatic cancer in rats. At noncytotoxic concentrations, FM and its major congener, 2,2',4,4',5-5'-hexabromobiphenyl (HBB) inhibit intercellular communication in vitro, a property associated with known tumor promoters. The purposes of this study were to assess the in vivo capacity of PBB to promote hepatocarcinogenesis and to evaluate the reliability of the in vitro assays. FM BP-6 and HBB were compared with phenobarbital (Pb), in a two-stage model for hepatocarcinogenesis devised by Pitot and associates. Female Sprague-Dawley rats weighing 200-250 g were injected ip with 10 mg/kg of diethylnitrosamine (DEN) 24 hours after a 2/3 partial hepatectomy (PH). Thirty days after Ph, groups of 6 rats were fed a control diet or diets containing Pb, FM BP-6, or HBB. Rats not partially hepatectomized or given DEN were fed Pb, FM BP-6 or HBB at the same levels. At 6 months rats were killed and tissue samples were collected for histologic and histochemical studies. Enzyme altered foci were identified by using gamma-glutamyl transpeptidase. FM BP-6 caused decreased weight gain, thymic atrophy and enlarged and vacuolated hepatocytes. (no Refs)

52. IDENTIFICATION OF CYSTEINE AND METHIONINE ADDUCTS FORMED BY REACTIONS WITH 2,2',5,5'-TETRACHLOROBIPHENYL-3,4-OXIDE (TCB-O) IN VITRO (MEETING ABSTRACT).

Preston BD, Miller JA, Miller EC
McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, WI, 53706
Proc Am Assoc Cancer Res; 23:238 1982

TCB (2,2',5,5'-Tetrachlorobiphenyl), a major component of the hepatic tumor promoting agent Aroclor 1254, is metabolized in the rat via TCB-O. TCB undergoes metabolism-dependent binding to proteins and is converted to methylsulfide and methylsulfone derivatives in rodents. We have used uv, infra-red, 1H-nuclear magnetic resonance, and mass spectral techniques to characterize the products formed from reactions of TCB-O with L-cysteine and N-acetyl-L-methionine in vitro. Incubations of TCB-O with L-cysteine in ethanol:Tris buffer solution at pH 7.4, 37 C gave rise to 6% reaction of TCB-O in 25 hr to form a single product peak isolated by high pressure liquid chromatography. This peak was identified as a mixture of 3-and 4-(cysteine-S-yl)-TCB in about a 1:1 ratio. When TCB-O was reacted with L-cysteine in dimethyl sulfoxide:phosphate buffer solution (pH 7.4, 37 C), four additional product peaks were formed. Three of these minor products have been partially characterized as a (cystein-S-yl)-dihydro-hydroxy-TCB, a (TCBthio)-TCB, and a (TCBthio)-dihydro-hydroxy-TCB. Incubations of TCB-O with N-acetyl-L-methionine in ethanol:Tris buffer solution at pH 7.4, 37 C gave rise to 0.3% reaction of TCB-O in 48 hr to form equal amounts of 3-and 4-(methylthio)-TCB. Methylsulfonyl-TCBs were not detected in these reactions. These results suggest that TCB-O may be a metabolic intermediate of TCB responsible for protein binding and the formation of methylthio-TCB metabolites in vivo. (2 Refs)

53. HALOGENATED BIPHENYLS AS AHH INDUCERS: EFFECTS OF DIFFERENT HALOGEN SUBSTITUENTS.

Bandiera S, Sawyer T, Campbell MA, Robertson L, Safe S
(c/o Safe) Dept. Veterinary Physiology and Pharmacology, Texas A and M Univ., College Station, TX, 77843
Life Sci; 31(6):517-525 1982

The analogs 4'-iodo-2,3,4,5-tetrachlorobiphenyl, 4'-bromo-2,3,4,5-tetrachlorobiphenyl, 4'-chloro-2,3,4,5-tetrachlorobiphenyl and 4'-fluoro-2,3,4,5-tetrachlorobiphenyl were adminstered to immature male Wistar rats and the effects of this homologous series of 4'-halo-2,3,4,5-tetrachlorobiphenyls on the microsomal drug-metabolizing enzymes were determined. All the halogenated biphenyls increased microsomal benzo[a]pyrene hydroxylase (or aryl hydrocarbon hydroxylase, AHH), ethoxyresorufin (ER) O-deethylase and dimethylaminoantipyrine (DMAP) N-demethylase. The effects of the 4'-halo-2,3,4,5-tetrachlorobiphenyls on the microsomal enzyme activities and on the relative peak intensities and spectral shifts of the reduced cytochrome P-450:CO and ethylisocyanide (EIC) binding difference spectra were similar to those observed after coadministration of phenobarbitone (PB) and 3-methylcholanthrene (MC). The relative activities of the halogenated biphenyls were determined using two in vitro assays; namely cytochrome P-448 associated induction in rat hepatoma H-4-II E cells in culture and competitive binding to the hepatic cytosolic Ah receptor protein from male Wistar rats. The relative potencies of the 4'-halo-2,3,4,5-tetrachlorobiphenyls followed the order I greater than Br greater than Cl greater than F for both assays and differences in the EC50 values for the iodo and fluoro analogs were greater than three orders of magnitude for ER O-deethylase induction in rat hepatoma cells in culture. One possible explanation for these effects may be associated with differences in the polarizability of the laterally substituted halogen groups. However, other differences in the physico-chemical properties of the halogen atoms may also be important. (27 Refs)

54. RENAL TOXICITY AND TUMORIGENICITY OF HEXACHLOROBENZENE (HCB) IN RATS (R) (MEETING ABSTRACT).

Lambrecht RW, Erturk E, Grunden EE, Headley DB, Peters HA, Morris CR, Bryan GT

Department of Human Oncology and Neurology, University of Wisconsin Center for Health Sciences, Madison, WI, 53792

Proc Am Assoc Cancer Res; 23:210 1982

HCB, a fungicide and by-product of chlorinated hydrocarbon synthesis, has been reported to be a rodent hepatocarcinogen. It was fed to both sexes of R at doses of 0, 200, and 400 ppm for 90 days. On the 91st day, 25/50 R from each group were killed, necropsied, and histologically examined. The remaining 25 R were fed HCB-free diet and were killed at 6-wk intevals thru the 424th day. Growth rate and food consumption were not significantly different between control and test groups except in the final stages of study. In addition to liver neoplasms and generalized lymphatic leukemias, a variety of renal lesions were observed. These included parenchymal degeneration and hyalinous casts (D and C), nephritis and infarcts (N and I), renal cell adenoma (RCA) and carcinoma (RCC). (no Refs)

55. HEPATOTOXICITY AND TUMORIGENICITY OF HEXACHLOROBENZENE (HCB) IN SYRIAN GOLDEN HAMSTERS (H) AFTER SUBCHRONIC ADMINISTRATION (MEETING ABSTRACT).

Lambrecht RW, Erturk E, Grunden E, Headley DB, Morris CR, Peters HA, Bryan GT

University of Wisconsin Center for Health Sciences, Madison, WI, 53792

Fed Proc; 41(3):329 1982

HCB, a rodent carcinogen, is a by-product of chlorinated hydrocarbon synthesis and used as a fungicide. It was fed to both sexes of H at doses of 0, 200, and 400 ppm for 90 days. On the 91st day, 25/50 H from each group were killed, and histologically examined. The remaining 25 H were fed HCB-free diet and sacrificed at 6-week intervals through day 361. Growth and food consumption did not differ between control and exposed H. Liver was the most severely involved organ exhibiting a variety of precirrhotic (PC) and cirrhotic (C) lesions, bile-duct hyperplasia (BDH), and hepatomas (HEP). (no Refs)

56. COMPETITIVE HYDROCARBON INDUCTION OF AHH IN C3H/10T1/2 CELLS (MEETING ABSTRACT).

Ho D, Gill K, Fahl WE

Department of Pharmacology-Cancer Center, Northwestern University Medical School, Chicago, IL, 60611

Proc Am Assoc Cancer Res; 23:325 1982

We are studying the relative abilities of benz(a)anthracene (BA), 3-methylcholanthrene (3MC) and TCDD (2,3,7,8-tetrachlorodibenzoparadioxin) to induce cyt-P450 dependent benzo(a)pyrene metabolism (AHH (arylhydrocarbon hydroxylase)) in cultures of transformable C3H/10T1/2 mouse embryo fibroblasts. BA was found to be the most effective inducer of the three compounds; 13 uM BA (24 hr exposure) elicited a 7-10 fold increase in AHH activity. 10-7M TCDD gave a 2-fold induction, and no AHH increase was seen after exposure of the cells to 13 uM 3MC. All three compounds markedly induced C3H mouse liver AHH activity. As we and others have reported, the extent of induction seen in the 10T1/2 cell cultures was dependent upon the degree of cell confluence. Increasing concentrations of 3MC were able to totally suppress the induction seen with 13 uM BA alone in a dose related manner. Significantly higher concentrations of 3MC were required to suppress the induction when 26 uM BA was added to the medium. Based on these data, 3MC may be acting as a competitive antagonist (without eliciting a 3MC agonist reponse) at a receptor which mediates BA induction in these cells, or 3MC metabolites may be sufficiently toxic in these cells to prevent a normal induction response. (no Refs)

57. MECHANISMS CONTROLLING EXCRETION OF BENZO(A)PYRENE AND ITS METABOLITES BY THE SOUTHERN FLOUNDER, PARALICHTHYS LETHOSTIGMA (MEETING ABSTRACT).

Pritchard JB, Frech ME, Bend JR, Niehs CV

Whitney Laboratory, St. Augustine, FL, 32084

Fed Proc; 41(3):1545 1982

Marine teleosts extensively metabolize polycyclic aromatic hydrocarbons (PAH) via the cytochrome P-450 mixed function oxidase system. In contrast to mammals, a much greater fraction, approximately 60%, of the metabolism of the model PAH, benzo(a)pyrene (BP), occurs at the benzo-ring. Metabolism in this region of the molecule yields metabolites which have been shown to be toxic, ie carcinogenic, mutagenic. Following injection of 2.5 umol/kg radiolabelled BP, BP-7-phenol, BP-1-phenol, or BP-7,8-trans-dihydrodiol, the clearance of each compound exceeded the simultaneously measured glomerular filtration rate, thus, demonstrated net tubular secretion. Clearance of label following BP-7,8-diol administration exceeded that following the phenol metabolites by 10 fold and was more than 30 times the initial clearance after injection of BP itself. Analysis of the urine by TLC (thin layer chromatography) and HPLC (high pressure liquid chromatography) indicated that 100% of the urinary radioactivity was found in polar metabolites of the initial compound, predominantly glucuronide and sulfate conjugates. Secretion was blocked by probenecid, the classical inhibitor of the organic anion transport system. Finally, it was shown that other organic anions including the herbicide, 2,4-D, were very effective inhibitors of the secretion of these PAH metabolites, suggesting that these 'less toxic' anions might potentiate PAH toxicity by prolonging their retention and promoting bioconcentration. (no Refs)

BENZENE DERIVATIVES

58. ZYMBAL GLAND CARCINOMAS IN RATS FOLLOWING EXPOSURE TO BENZENE BY INHALATION.

Maltoni C, Cotti G, Valgimigli L, Mandrioli A
Viale Ercolani, 4/2 40138 Bologna, Italy
Am J Industr Med; 3(1):11-16 1982

Pregnant Sprague-Dawley rats were exposed by inhalation to benzene (200 ppm, 4 hr/day, 5 days/wk) from day 12 of pregnancy up to delivery, and the offspring were exposed to 200-300 ppm for 4-7 hr/day, 5 days/wk for 15 or 104 wk. Results at 86 wk are reported. Of the 269 treated rats, 227 were still alive and of the 307 control rats, 256 were still alive. Zymbal gland carcinomas were seen in five male and five female rats exposed to benzene, compared with only one female control. The tumors had sebaceous, squamous, and tubular patterns and metastasized to the regional lymph nodes, lungs, and brain. (3 Refs)

59. BUTYLATED HYDROXYTOLUENE: TUMOR-PROMOTING ACTIVITY IN AN IN VITRO TWO-STAGE CARCINOGENESIS ASSAY.

Djurhuus R, Lillehaug JR
Dept. Biochemistry, Univ. Bergen, Arstadveien 19, 5000 Bergen, Norway
Bull Environ Contam Toxicol; 29(1):115-120 1982

An in vitro two-stage carcinogenesis test using mouse embryo fibroblasts C3H/10T1/2 clone 8 was employed to assess the possible role of butylated hydroxytoluene (BHT) as a tumor promoter. BHT was not toxic to the cells over the concentration range 10(-7) to 10(-4) M. In vitro transformation experiments showed high frequencies of transformation with a transforming dose of 20-methylcholanthrene (MCA: 0.37 uM) and with a low initiating dose (0.037 uM) and repeated treatment with 12-O-tetradecanoyl phorbol-13-acetate. Some groups of cells cultures contained type III foci, suggesting that BHT has the capacity to enhance the transformation frequency in C3H/10T1/2 cells. Statistically significant increases in transformation frequency were apparent at all three concentrations of BHT (1, 5, and 10 uM), suggesting that BHT might act as a cocarcinogen with MCA. Data obtained for BHT in the present study resemble those recently reported for saccharin; on a molar basis the cocarcinogenic potency observed for BHT was approx 1,000x that of saccharin. (10 Refs)

60. STUDIES ON CHEMICAL CARCINOGENS. XXI. QUANTITATIVE STRUCTURE-MUTAGENICITY RELATIONSHIP AMONG SUBSTITUTED STYRENE OXIDES.

Tamura N, Takahashi K, Shirai N, Kawazoe Y
Faculty Pharmaceutical Sciences, Nagoya City Univ., Tanabedori, Mizuho-ku, Nagoya 467, Japan
Chem Pharm Bull (Tokyo); 30(4):1393-1400 1982

The relationships between structure and mutagenicity of styrene and eight substituted styrene oxides were studied using the mutagenicity assay on Salmonella typhimurium TA100. Mutagenicity and cytocidal activity were correlated with molecular characteristics. Multiple regression analysis indicated that mutagenicity could be described by a combination of the reactivity of the epoxide group and the log of the Van der Waals volume of the molecule. Cytocidal activity depended only on the partition parameter of the molecule. (21 Refs)

DRUGS, COSMETICS, DETERGENTS AND OTHER COMMERCIAL MATERIALS

61. COMPARATIVE PHOTOBIOLOGY OF PSORALENS.

Ashwood-Smith MJ, Natarajan AT, Poulton GA
Environmental Toxicology Res. Group, Dept. Biology, Univ. Victoria, P.O. Box 1700, British Columbia V8W 2Y2, Canada
JNCI; 69(1):189-197 1982

The comparative photobiological effects of several fucocoumarins [ie, angelicin, psoralen, 8-methoxypsoralen (8-MOP), and 5-methoxypsoralen (5-MDP)] have been evaluated in a number of biological systems. The photosensitized induced lethality and genetic damage have been assessed in bacterial, animal, and human cells, and the rank order of effectiveness established psoralen as the most active compound followed by 8-MOP, 5-MOP, and angelicin. 5-MOP and 8-MOP are, however, essentially equally active in the production of chromosome damage in human cells in vitro. (Author abstract) (15 Refs)

62. PSORALENS ARE NOT MUTAGENIC IN THE SALMONELLA ASSAY (MEETING ABSTRACT).

Rao TK, Allen BE, Cox JT
Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN, 37830
Med Pediatr Oncol; 10(1):100 1982

Psoralens are the most notable photosensitizing agents with clinical use for the treatment of skin diseases. Photochemical interaction with the pyrimidine bases of DNA is the basis for their biological activity, which raises the possibility of adverse effects such as toxicity, mutagenicity, carcinogenicity and chromosomal aberrations. Sufficient evidence exists to show that 8-methoxypsoralen (8-MOP), followed by exposure to near UV light (NUV) causes tumors in albino mice, sister chromatid exchange in lymphocytes, and mutations in microbial assays. Psoralens are not adequately studied in the Salmonella assay. Our studies indicated a lack of mutagenic activity for 8-MOP and trioxsalen even when metabolically activated, which is contrary to the report of Bridges and Mottershead that 8-MOP caused frameshift mutations in the dark. Exposure to NUV following treatment with 8-MOP or trioxsalen of stationary or log phase cells did not show mutagenic activity. However, a dose-dependent (7.5-25 x 10(3) J/m2 from a Westinghouse F40BLB lamp) cytotoxicity was noted with strains deficient (TA98 and TA100) for UV-excision repair. Strains capable of UV-excision repair (TA1978 and TA1975) were less sensitive in the cytotoxicity assay. This suggests a genetic nature of the damage. These studies indicate the inability of the Ames Salmonella assay to detect 8-MOP (a possible carcinogen) as a mutagen. (1 Ref)

63. PROMOTION BY PHENOBARBITAL (PB) OF CARCINOGENESIS INITIATED BY N-[4-(5-NITRO-2-FURYL)-2-THIAZOLYL]FORMAMIDE (FANFT) (MEETING ABSTRACT).

Wang CY, Garner CD, Hirose M
Michigan Cancer Foundation, Detroit, MI, 48201
Proc Am Assoc Cancer Res; 23:403 1982

The present study investigated whether FANFT also initiates liver tumors and PB promotes bladder tumors. Weanling male Fischer rats were divided into 4 groups: I, fed Wayne Lab Blox for 7 wks followed by AIN (American Institute of Nutrition)-76 diet; II, fed the same as I except that the AIN

Diet contained 0.05% PB; III, fed Wayne diet containing 0.2% FANFT for 6 wks, followed by 1 wk with Wayne diet, and then by AIN diet; and IV, fed the same as III except that the AIN diet contained 0.05% PB. The experiment was terminated at the end of 93 wks. Rats in III and IV ingested approx 1.2 g FANFT each. The effective number of rats were 27 (I), 24 (II), 40 (III), and 42 (IV), and survival times (wks) were 90 (I); 86 (II); 89 (III); and 87 (IV). The number of rats bearing bladder papillomas and carcinomas, respectively, were 4 and 17 (III), and 4 and 28 (IV). The incidence of bladder carcinomas in IV was significantly greater than in III. Neither I nor II had bladder tumors. The number of rats bearing hepatic cellular-altered foci and neoplastic nodules, respectively, were: 4 and 0 (I); 8 and 1 (II); 7 and 1 (III); and 23 and 6 (IV). The number of hepatic gamma-glutamyltranspeptidase (GGT) foci/cm2 were: 0.12 (I); 1.40 (II); 0.28 (III); and 5.52 (IV) in the rats surviving to the 93rd wk. The number of GGT foci in IV was significantly greater than in the other groups. (no Refs)

64. EFFECT OF THE DRUGS METHAPYRILENE AND NAFENOPIN ON CARCINOGEN-INDUCED ALTERED FOCI IN RAT LIVER (MEETING ABSTRACT).

Furuya K, Furukawa K, Mori H, Williams GM, Levine W
Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Proc Am Assoc Cancer Res; 23:400 1982

Methapyrilene, an antihistimine and nafenopin, a hypolipidemic agent, have produced liver tumors in rodents, but have shown no evidence of genotoxicity. To determine if these drugs could act as liver tumor promoters, they were fed at 0.05 and 0.1% to F344 rats for up to 24 weeks after the induction of hepatic altered foci by feeding of 0.02% N-2-fluorenylacetamide (FAA) for 8 weeks. The effect of the drugs on FAA-induced altered foci identified by resistance to iron accumulation (IR) and gamma-glutamyl transpeptidase (GGT) activity was compared to that of the liver tumor promoter phenobarbital which enhances the progression of foci to neoplasms. Like phenobarbital, methapyrilene at 0.1% increased the numbers of both IR and GGT-positive foci (6x and 3x respectively) and neoplastic nodules (10x), but not carcinomas, relative to rats returned to the control diet. Nafenopin at 0.1% decreased the numbers of GGT-positive foci by more than 0.3 although IR foci were almost the same as in controls. The number of neoplastic nodules was also reduced by more than 0.5 in the nafenopin group. Thus, methapyrilene like phenobarbital displayed a substantial enhancing effect on hepatocarcinogenesis following FAA while nafenopin was inhibitory. (no Refs)

65. INHIBITION OF DNA METHYLTRANSFERASE ACTIVITY BY A RANGE OF PROXIMATE CARCINOGENS (MEETING ABSTRACT).

Wilson VL, Jones PA
Childrens Hospital of Los Angeles, Los Angeles, CA, 90054
Proc Am Assoc Cancer Res; 23:259 1982

We have recently developed a method for the production of hemimethylated DNA, which can serve as an efficient methyl acceptor in a DNA-methyltransferase assay system. This hemimethylated DNA was used to determine the effects of DNA modification and adduct formation by proximate carcinogens, on in vitro enzymatic methylation of cytosine residues in DNA. Mouse spleen DNA-methyltransferase activity was markedly decreased by alkylation of hemimethylated DNA with prototypes from several classes of chemical carcinogens. Pretreatment of hemimethylated DNA with nitrogen mustard or melphalan, at a molar ratio of 0.2, resulted in a more than 50% inhibition of DNA methyltransferase activity. On a molar basis, benzo[a]pyrene diolepoxide and N-acetoxy-N-acetyl-2-aminofluorene were approximately one-tenth as potent as nitrogen mustard. The ethylating and methylating agents were the least potent in this inhibitory action. Extensive dialysis of the alkylated substrate DNA did not alter the subsequent inhibition of DNA-methyltransferase activity. Thus the formation of DNA adducts can effectively attenuate the enzymatic methylation of DNA in vitro. However, direct modification of the DNA-methyltransferase enzyme by some of these alkylating agents, was also found to significantly inhibit enzymatic activity. (1 Ref)

66. EVALUATION OF POTENTIAL CARCINOGENICITY OF CIODRINE.

Didenko GG, Gupalovich TD, Petrovskaia OG

All-Union Res. Inst. Hygiene and Toxicology, Pesticides,, Polymers, and Plastics Kiev, USSR

Gig Sanit; (7):83-84 1982

Potential carcinogenicity of acaricide ciodrine (O,O-dimethyl-O,1-methyl-2 (phenylcarbethoxy)vinylphosphate) was studied in random-bred mice and rats. The animals were subjected to intragastric administration of ciodrine (6 mg/kg in mice and 10.7 mg/kg in rats, 2x/wk, for 18 wk). Duration of the experiment was 72 wk (mice) or 78 wk (rats). The incidence of ciodrine-induced tumors in mice was 16.5% (23.9% in females and 10.3% in males), compared with 20.9% in nontreated controls. The incidence of ciodrine-induced tumors in rats was 8.1% (7% in females and 9.2% in males), compared with 9.6% in controls. Both ciodrine-treated and control mice and rats developed benign and malignant tumors of the lung, mammary gland, and hematopoietic organs. This experiment failed to demonstrate the carcinogenic activity of ciodrine. (3 Refs) (In RUS)

67. CARCINOGENIC EFFECT OF VARIOUS SURFACTANTS USED IN COMMERCIAL SYNTHETIC DETERGENTS.

Ianysheva NIa, Voloshchenko OI, Chernichenko IA, Balenko NV

A. N. Marzeev Res. Inst. General and Community Hygiene, Kiev, USSR

Gig Sanit; (7):9-12 1982

Potential carcinogenic activity of various surfactants, which were used in the manufacturing of the commercial synthetic detergents, was studied in CC57W mice. In acute experiment, the animals received applications of 12% aqueous emulsion of Sulfanol chloride and Synthanol DS-10 (5x/wk, 30 applications). Animals were sacrificed 1 day after the last application, and the number of sebaceous glands was determined. The av number of sebaceous glands per 100 hair follicles in the mice treated with Sulfanol chloride was 70.35, compared with 80.8 in the mice exposed to Synthamide DS-10 and 82.75 in controls. In chronic experiment, animals received single application of benzo(a)pyrene followed by applications of Sulfanol chloride or sodium alkylsulfate (3-5x/wk, for 12 mo, total dose of test compounds of 2,850 mg/kg). Chronic exposure to Sulfanol chloride produced focal proliferation of fibroblasts, lymphocytic infiltration of the derma, and squamous cell carcinomas of the sebaceous glands. Applications of alkylsulfate produced atrophy and mild hyperplasia of epithelium. (8 Refs) (In RUS)

68. PROMOTION OF LUNG TUMORS IN MICE.

Witschi HP

Oak Ridge Natl. Lab., Oak Ridge, TN

Proceedings of the EPA/HERL International Symposium on Health Effects of Tumor Promotion, held in Cincinnati, Ohio, October 13, 1981. Available from National Technical Information Service, Springfield, VA, as DE82001498:, 26 pp., 1981.

Several elements of two-stage carcinogenesis apply to the development of lung tumors in mice. At least three agents, identified as promoters, will also enhance tumor formation in lung: phorbol, saccharin, and butylated hydroxytoluene (BHT). The antioxidant BHT is effective only if animals are treated after exposure to an initiating agent. Administration can be delayed up to 5 mo after urethan treatment and still enhance tumor formation. BHT enhances lung tumor formation regardless of its route of administration. The lowest dose required to produce an effect has not yet been determined. in at least one mouse strain, BHT also enhances tumor formation in animals initiated with 3-methylcholanthrene or diethylnitrosaine. No evidence is available yet to show that BHT would enhance tumor development in animals treated with subcarcinogenic doses of an initiating compound. Nor has it been possible to produce more tumors with BHT in mouse strains which have a low spontaneous tumor incidence and respond poorly to urethan. Nevertheless, the data collected on the effects of BHT on mouse lung tumor development have broadened the concept of two-stage carcinogenesis and complement the evidence for initiation-promotion available for other epithelial tissues. (Author abstract)

69. DAUNORUBICIN (D) INDUCED MAMMARY TUMORS IN FEMALE SPRAGUE-DAWLEY RATS AND THE ROLE OF ALPHA-TOCOPHEROL (ALPHAT) AS A MODIFIER TO THE CARCINOGENESIS (MEETING ABSTRACT).

Wang YM, Howell SK, Tsai CC, Van Eys J

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Proc Am Assoc Cancer Res; 23:352 1982

Second malignancies are significant side effects of cancer chemotherapy. Anthracycline antibiotics-induced tumors have been recognized in rats and monkey. We have, recently, investigated the activity of alphaT as a potential modifier to the carcinogenecity-induced by D in female rats. Two groups of rats at age 40 day (less than 125 g) and 48-56 days (150-200 g) respectively were used. In older animals, D (10 mg/kg) injected intravenously induced tumors in 50% (11/22) of the animals. Preinjection with alpha-tocopheryl acetate (alphaTA, 300 mg/kg/day) daily for consecutive 4 days prior to the injection of D reduced significantly the tumor incidence (2/16). In younger animals, tumor incidence was less (5/21) and the pretreatment with the vitamin did not modify the tumor development (9/27). In older animals, organ distribution of 3H-D and 14C-alphaTA changes by each other, however, alphaTA does not alter the concentration of D in mammary tissue and fat. However, in single mammary epithelial cells suspensions isolated in rats after 4 daily treatment of alpha-TA or placebo, the intracellular D distribution was significantly modified in the presence of alphaT and alphaTA. The concentration of 3H-D in nuclear fractions was 30-40% in those cells isolated from alphaT treated animals as compared to the cells from placebo treated animal. It appears the alteration of subcellular D distribution by the vitamin may play a role in the modification of D-induced mammary tumor in rats. (no Refs)

REVIEWS AND OTHER COMPOUNDS

70. DETECTION OF CARCINOGENS WHICH INITIATE THE PROCESS OF C3H/10T1/2 CELL TRANSFORMATION (MEETING ABSTRACT).

Boreiko CJ, Abernethy DJ, Frazelle JH
Chemical Industry Institute of Toxicology, Research Triangle Park, NC, 27709
Proc Am Assoc Cancer Res; 23:285 1982

It is known that Formaldehyde, N-methyl-N'-nitro-N-nitrosoguanidine and aflatoxin B1 initiate the process of C3H/10T1/2 transformation, producing transformed foci only when treated cells are subsequently exposed to the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA). Studies were conducted to establish whether initiation of transformation is a common consequence of exposure to chemical carcinogens. Cell culture conditions optimal for the detection of initiating agents were determined and the ability of carcinogens to transform or initiate transformation examined. Treatment with cytotoxic concentrations of N-nitrosomethylurea, N-nitrosoethylurea, methylmethanesulfonate and ethylmethanesulfonate followed by continuous exposure to 0.25 ug/ml TPA produced foci in at least 25% of the dishes exposed to the highest concentration of each compound. Foci were generally not observed in dishes exposed to TPA alone or in chemically treated dishes not exposed to TPA. Mitomycin C, 5-fluorodeoxyuridine, amethopterin and 5-azacytidine, alone produced foci in 4-47% of treated dishes and exposure to TPA enhanced focus frequency more than two-fold. In the absence of TPA, 3-methylcholanthrene and benzo(a)pyrene produced foci in 50-100% of treated dishes. TPA caused 50% and 22% reductions in focus formation by 3-methylcholanthrene and benzo(a)pyrene respectively. These studies indicate that some classes of carcinogens function as initiating agents in the standard C3H/10T1/2 transformation protocol and that the presence of TPA can significantly enhance the sensitivity of this system to genotoxic substances. (no Refs)

71. 3-AMINOBENZAMIDE SYNERGISTICALLY INCREASES SISTER-CHROMATID EXCHANGES IN CELLS EXPOSED TO METHYL METHANESULFONATE BUT NOT TO ULTRAVIOLET LIGHT.

Morgan WF, Cleaver JE
Lab. Radiobiology and Environmental Health, Univ. California, San Francisco, San Francisco, CA, 94143
Mutat Res; 104(6):361-366 1982

The effects of 3-aminobenzamide on the production of sister-chromatid exchanges induced by methyl-methanesulfonate (MMS) and UV light in Chinese hamster ovary cells (CHO) and Simian virus 40 (SV40)-transformed human cells (GM637) were investigated. Synergism between 3-aminobenzamide and MMS was observed, while no significant effect was seen with 3-aminobenzamide and UV light in either cell type. (25 Refs)

72. MODIFICATION OF DEOXYRIBONUCLEIC ACIDS BY ALKYLATING AGENTS (MEETING ABSTRACT).

DaSilva Gomes J, Narayan R, Douthit L, Chang C
Department of Medicinal Chemistry, Purdue University, West Lafayette, IN, 47906
Proc Am Assoc Cancer Res; 23:258 1982

The covalent interactions between deoxyribonucleic acid (DNA) and alkylating agents have been considered to be critical in the understanding of the mechanisms of their mutagenic and carcinogenic actions. We report here the studies on the methylation of DNA by methyl methanesulfonate (MeMS) using reverse-phase high pressure liquid chromatography (HPLC). The methylated DNA was degraded by phosphodiesterase and alkaline phosphatase at pH 7.0 to mononucleosides, and then separated by C18-silica gel column eluted with a solution of ammonium phosphate (0.01M), tetramethylammonium chloride (5.5mM) and acetonitrile (3%). The development of this separation method was guided by a parallel study using a non-destructive carbon-13 nuclear magnetic resonance (13CNMR) method. This direct method permitted us to evaluate the enzymic degradation conditions, the stability of the methylated products and the optimal HPLC separation conditions. The DNA modification products were identified on the basis of the retention times of the synthetic model compounds and the absorbance ratios at 254nm and 280nm. In the reaction of salmon sperm DNA with MeMS at pH 7.0 for 6 hr, four products were detected: 1-methyldeoxyadenosine (26.8%), 7-methyldeoxyguanosine (37.1%), 3-methyldeoxycytidine (28.8%) and 7-methylguanine (7.3%). No significant amount of 3-methyldeoxyadenosine was observed. These HPLC results were in good agreement with the direct 13CNMR results. (no Refs)

73. TWO-STAGE CARCINOGENESIS ON SKIN AND IN INTERNAL ORGANS OF C57BL/B6 MICE (MEETING ABSTRACT).

Yamasaki H, Cabral JR, Galendo D, Tomatis L
International Agency for Research on Cancer, Lyon, France
Toxicologist; 2(1):63 1982

Promoting effect of phorbol esters, as represented by 12-O-tetradecanoyl phorbol-13-acetate (TPA), has been extensively studied on mouse skin, using a conventional initiation-promotion protocol. Since it has been shown that these tumor promoters exert a variety of biological and biochemical effects on the cells derived from various tissues other than mouse skin, it was of our interest to examine the promoting activity of TPA on internal organs as well as on skin. When fifty C57BL/B6 mice, 6 week old, were painted once with 3 mg of benzo(a)pyrene (B(a)P) and painted with 5 ug of TPA twice a week, 64% of mice developed papillomas by 30 weeks of treatments, whereas none of control groups, treated with B(a)P alone or TPA alone, developed papillomas. These results confirm that C57BL/B6 mice are reasonably sensitive to a conventional two-stage carcinogenesis protocol. However, when the same amount of B(a)P was injected subcutaneously to pregnant mothers and their descendants were painted on skin of the back with 5 ug of TPA twice a week from weaning for 93 weeks, no persistent papilloma was observed. Similarly, the transplacentally exposed mice were injected intraperitoneally with 5 to 10 ug of TPA twice a week. After 100 weeks, the number of mice that died with tumor (4/63) was not significantly different from that in the group without TPA injection (3/64). Taken together, these results suggest that under the experimental conditions used, a conventional mouse skin initiation-promotion carcinogenesis is demonstrable, but transplacental initiation-postnatal promotion of skin and internal organs has not been clearly observed so far in C57BL/B6. (no Refs)

74. FAILURE OF PHORBOL ESTER TPA TO PROMOTE GROWTH OF IN VIVO-INITIATED RAT HEPATOCYTES TRANSFERRED INTO A CULTURE SYSTEM.

Kayano T, Nomura K, Hino O, Kitagawa T
Dept. Pathology, Cancer Inst. Tokyo, Kami-Ikebukuro 1-37-1, Toshima-ku, Tokyo 170, Japan
Gan; 73(3):354-357 1982

The effect of 12-O-tetradecanoylphorbol-13-acetate (TPA), a potent promoter in epidermal carcinogenesis, on the growth of rat hepatocytes initiated in vivo and transferred into a culture system was investigated. The hepatocytes were isolated by enzymatic perfusion from the rat liver after 12 wk of acetylaminofluorene feeding or 2 to approx 6 wk of diethylnitrosamine treatment. TPA did not show any promotive effect in terms of the number and size of proliferative epithelial cell foci derived from initiated hepatocytes, in contrast to the remarkable effect of phenobarbital, which is a potent promoter in hepatocarcinogenesis. The results suggest the existence of organ or target cell specificity of promoters in the two-stage concept of carcinogenesis. (Author abstract) (16 Refs)

75. ORIGIN AND FORMATION OF 1,7-DIMETHYLGUANOSINE IN TRNA CHEMICAL AND ENZYMATIC METHYLATION.

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Biochim Biophys Acta; 697(3):336-343 1982

The tRNA chemical methylation: (1) 1,7-Dimethylguanosine was found in in vivo methylated tRNA from liver and kidney of rat after exposure to a low dose of dimethylnitrosamine (4 mg/kg body weight). (2) At 4 h after dimethylnitrosamine administration, the 1,7-dimethylguanosine:7-methylguanine ratio (product ratio) for liver and kidney tRNA was 0.017 and 0.091, respectively. At 24 h after dimethylnitrosamine administration, the product ratio was lower in both hepatic and renal tRNA. (3) When dimethylnitrosamine was given in four separate daily injections, the product ratio in hepatic tRNA 4 h after the last dose was the same as for the same total dose given by a single injection, but in renal tRNA it was lower. No dialkyl compound was found in liver and kidney tRNA 24 h after the last multiple injection. tRNA enzymatic methylation: (1) Base analyses of Escherichia coli B tRNA methylated in vitro, by using S-adenosylmethionine as physiological methyl donor and enzyme preparations from liver and kidney of normal rat, indicated that 1,7-dimethylguanosine was also a product of enzymatic methylation. (2) The amount of 1,7-dimethylguanosine formed by kidney enzyme preparation was 3x that produced by the liver extract. (3) A second type of enzymatic methylation assay where chemically methylated tRNA was used as substrate indicated that the 7-methylguanine residues in the nucleic acid are not the substrate of the methylase activity forming the 1,7-dimethylguanosine moieties. Analogous data were obtained for the origin of 1,7-dimethylguanosine residues in tRNA chemical methylation by dimethyl sulfate. (Author abstract) (30 Refs)

76. MODULATION OF THE DIFFERENTIATIVE PROCESS IN HUMAN KERATINOCYTES CREATING RESPONSIVE POPULATIONS TO A CARCINOGENIC INSULT (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:302 1982

We reported last year on the transformation of human keratinocytes. Subsequent to those experiments we separated the layers of the skin from the stratum basalis leaving the stratum basalis attached to the plastic substratum. This was accomplished by treating seven day old cultures with 0.25% collagenase and 0.02% ethyleneglycol tetracetic acid (EGTA) dissolved in minimal essential medium minus calcium and magnesium for a few minutes. Treatment of this layer with either Propane sultone or UV254nm or other carcinogens resulted in populations that either exhibited anchorage independent growth and cellular invasiveness or cornified. Treatment of the other layers of the 'skin' resulted in limited proliferation in soft agar, followed by cornification of the small colonies, 10-20 cells in number. These cells stained pink with Rhodanile blue. If we pretreated the stratum basalis with modulators, 12-O-tetradecanoylphorbol-13-acetate (TPA), anthralin insulin etc, the cells that composed the stratum basalis either synthesized keratin or did not. The cells exhibiting a fluorescent pattern characteristic of cytoplasmic keratin subunits went on to cornify. The other population, not exhibiting the fluorescent pattern responded to the carcinogenic insult and exhibited anchorage independent growth in soft agar and cellular invasiveness, on CES. (1 Ref)

77. IMPROVED TRANSFORMATION OF C3H10T1/2CL8 CELLS BY DIRECT-AND INDIRECT-ACTING CARCINOGENS (MEETING ABSTRACT).

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Carcinogenesis and Metabolism Branch, US Environmental Protection Agency, Research Triangle Park, NC, 27711

Proc Am Assoc Cancer Res; 23:284 1982

C3H10T1/2CL8 cells are transformed by a variety of structurally different chemicals, including polycyclic aromatic hydrocarbons, aromatic amines, and pyrimidines. It has been reported that C3H10T1/2CL8 cells are insensitive to the transforming effects of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) unless the cells are synchronized. This finding is particularly interesting because MNNG mutates C3H10T1/2CL8 cells to ouabain resistance without the need for cell synchrony. Aflatoxin B1 (AFB1) also does not transform C3H10T1/2CL8 cells under conditions described by Reznikoff et al. We report here that oncogenic transformation of C3H10T1/2CL8 cells can be improved by treating asynchronous cultures of cells 5 days after seeding. Benzo(a)pyrene-induced transformation was increased fourfold by this method, compared with treating the cells 1 day after seeding. MNNG produced an average of 1 focus/dish, with 61% of the dishes exhibiting foci, when administered 5 days after seeding. Propane sultone and AFB1 also produced marked transformation responses when administered 5 days after seeding. However, 4-dimethylaminoazobenzene and urethane did not induce transformation when administered either 1 day or 5 days after seeding. With all chemicals examined, clonal cytotoxicity was reduced when they were administered 5 days after seeding. (1 Ref)

78. INDUCTION OF NEOPLASTIC TRANSFORMATION AND SINGLE STRAND DNA BREAKS IN C3H 10T1/2 CELLS BY POLYCYCLIC HYDROCARBONS AND SHORT CHAIN ALKYLATING AGENTS (MEETING ABSTRACT).

Schechtman LM, Gallagher MA, Henry CJ, Kouri RE, Lubet RA

Microbiological Associates, Bethesda, MD, 20816

Fed Proc; 41(3):379 1982

The known carcinogens benzo(a)pyrene, BaP 7,8-diol, 3-methylcholanthrene, and 7,12-dimethyl benz(a)anthracene, all yielded striking dose-dependent transformation frequencies when tested in the standard 10T1/2 assay. In contrast, the two non-carcinogens anthracene and phenanthrene caused no transformation. The strong chemical carcinogen, dibenz(a,h)anthracene expressed weak transforming activity, while the weak carcinogen, benzo(e)pyrene expressed stronger activity. The short chain alkylating agents N-methyl-N'-nitro-N-nitrosoguanidine and ethyl methanesulfonate induced minimal transformation in the standard 10T 1/2 assay. However, it appears that modification of the assay by replating treated cells post-chemical treatment enhances the ability of the system to identify the short chain alkylating agents. We attempted to optimize carcinogen exposure employing a modified alkaline elution assay (which measures the production of single strand breaks). This test demonstrated few if any DNA strand breaks upon treament with transforming doses of BaP, or BaP-7,8-diol, whereas significant levels of strand breakage were observed following treatment with minimally toxic non-transforming doses of a number of short chain alkylating agents. (no Refs)

79. CURRENT APPROACHES TO THE EXPERIMENTAL INVESTIGATION OF CHEMICALS IN RELATION TO CANCER OF THE BRAIN.

Swenberg JA, Zimmerman HM, Maltoni C, Kurland L, Laerum OD, Kleihues P, Selikoff I, Heidelberger C

Chemical Industry Inst. Toxicology, Research Triangle Park, NC, 27709

Ann NY Acad Sci; 381:43-53 1982

Chemical induction of brain tumors, current methods for evaluating the carcinogenic potential of chemicals, and possible mechanisms of neuro-oncogenesis are reviewed. Chemical induction of brain tumors by polycyclic aromatic hydrocarbons, nitroso compounds, acrylonitrile, and other chemicals (1-aryl-3,3-dialkyltriazenes, 1,2-diethylhydrazine, azoethane, azoxyethane, and procarbazine) is described. Only a small number of chemicals that induce brain tumors have been identified by routine bioassays of new chemicals. Current guidelines require exposure of a minimum of 50 animals of each sex to 2-3 exposure levels and an equal number of controls. Complete necropsies, diagnosis by an experienced histopathologist, and confirmatory histochemical techniques are essential for properly classified brain tumors. Knowledge of normal variation in tumor incidence between species, strain, and sex is required. A positive bioassay should induce a significantly increased incidence of tumors in a dose-related manner. Possible mechanisms involved in neuro-oncogenesis have been proposed, including the formation and persistance of O6-alkylguanine in brain DNA of rodents and the occurrence of glial cell replication in the presence of promutagenic DNA damage. (48 Refs)

80. MUTAGENICITY AND NEPHROTOXICITY OF TWO TRIS(2,3-DIBROMOPROPYL)PHOSPHATE ANALOGUES: BIS(2,3-DIBROMOPROPYL)PHOSPHATE AND 2,3-DIBROMOPROPYLPHOSPHATE.

Soderlund E, Nelson SD, Dybing E
Dept. Toxicology, Natl. Inst. Public Health, Postuttak, Oslo 1, Norway
Acta Pharmacol Toxicol (Copenh); 51(1):76-80 1982

Mutagenicity and nephrotoxicity of two potential tris(2,3-dibromopropyl)phosphate (Tris-BP) metabolites, bis(2,3-dibromopropyl)phosphate (Bis-BP) and 2,3-dibromopropylphosphate (Mono-BP) were studied in male Wistar rats. Mutagenic activity (MA) was assayed in a quantitative modification of the Salmonella mutagenicity test using the TA100 tester strain. MA was expressed as His+ revertants/10(6) bacteria. Bis-BP and Mono-BP were clearly less mutagenic than Tris-BP when tested with liver microsomes from untreated or phenobarbital-pretreated rats at concentrations of 0.05 and 0.10 millimoles (mM). At 0.10 mM with phenobarbital microsomes, Bis-BP and Mono-BP induced 12.4% and 1.7% MA of Tris-BP, respectively. Animals, five in each group, received various doses (10, 25, 50, 100, 200 mg/kg) of Tris-BP and analogues as a single ip dose in dimethylsulfoxide (0.25 ml/100 g). The control group received vehicle alone. Both Bis-BP and Mono-BP were more nephrotoxic than Tris-BP in single dose experiments. Increased kidney/body wt ratios were found in all three compounds at the 200 mg/kg dose, although the increase with the Mono-BP analogue was not statistically significant. Histologically, tubular kidney necrosis was demonstrated in rats receiving 100 mg/kg Tris-BP or Mono-BP and higher and in animals administered 50 mg/kg Bis-BP and higher. For both Bis-BP and Mono-BP the degree of kidney necrosis was more extensive than for Tris-BP. No histological liver necrosis was observed in any of the treatment groups. Results indicated that the potential Tris-BP metabolites Bis-BP and Mono-BP are mutagenic and nephrotoxic, and in this respect mimic the parent compound. (16 Refs)

81. EFFECT OF FORMALDEHYDE ON DNA DAMAGE AND REPAIR IN HUMAN BRONCHIAL EPITHELIAL CELLS AND FIBROBLASTS (MEETING ABSTRACT).

Grafstrom RC, Fornace AJ, Harris CC
Laboratory of Human Carcinogenesis, National Cancer Institute, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:266 1982

The alkaline elution technique was used to study damage and repair of DNA in human bronchial epithelial cells (BE) and fibroblasts (BF), skin fibroblasts (SF) and XP12BE xeroderma pigmentosum (XP) skin fibroblasts. Exposure of cells to formaldehyde (HCHO) resulted in the formation of DNA-protein crosslinks (DPC) and DNA single strand breaks (SSB). All cell types showed a similar dose-response to HCHO with regard to the formation and disappearance of DPC. After exposure of the cells to doses between 0.1 ad 2.0 mM HCHO for 1 hr, the crosslinks were removed with a half-removal time of 2 to 3 hr. After 10 hr of post-treatment incubation, less than 10% of the DPC remained. In the presence of the repair polymerase inhibitors, 1-beta-D-arabinofuranosylcytosine and hydroxyurea, approximately 1 DNA SSB per 10(9) daltons accumulated in BF, BE, and SF cells in 4 hrs after treatment of the cells with 0.8 mM HCHO for 1 hr. In contrast, no SSB accumulated in XP cells with the same regimen of HCHO and polymerase inhibitors. These results indicate that HCHO induces DNA damage that is repaired by the UV-type excision repair pathway. A dose of 0.1 mM HCHO induce no detectable SSB in BE and BF. However, the same concentration of HCHO significantly inhibited the repair of x-ray-induced DNA SSB. A 5 to 10-fold higher concentration was required to inhibit unscheduled DNA synthesis induced by UV radiation or anti-benzo(a)pyrene diolepoxide. (no Refs)

82. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: THE RUBBER INDUSTRY.

IARC Working Group

Div. Environmental Carcinogenesis, International Agency for Res. on Cancer, Lyon, France

IARC Monogr Eval Carcinog Risk Chem Hum 28: 486 pp., 1982.

The carcinogenic risks of exposures to workers in the rubber industry is evaluated. Manufacturing of tires, and other rubber goods are considered with respect to exposures incident to the mixing of elastomers with chemicals and their subsequent conversion into finished products. An historical overview is presented with discussion of the origins of the rubber industry and the developing rubber industry and its occupational health hazards. Manufacturing processes are described for tires, tubes, remolds, and retreads; general rubber goods such as wire and cables, belting, hose, ebonite, rubber footwear, food processing equipment, aircraft deicing equipment, automobile parts; proofed rubber fabrics, adhesives and sealants; and dipped latex products and forms. The chemistry of rubber compounding is reviewed. Exposures in the workplace are discussed with respect to controls, protective equipment, work practices; studies of exposures in the workplace; and biological monitoring. Biological effects include carcinogenic, mutagenic, and teratogenic effects of exposure to accelerators, antioxidants, curing agents; solvents; monomers; talc; carbon blacks; aromatic amines; mineral oils, tar products and polycyclic aromatic hydrocarbons; nitroso compounds; phthalate and adipate esters; and curing fumes and other emissions. Effects in humans other than cancer including dermatologic respiratory, and reproductive, are discussed. Epidemiological studies of carcinogenicity in humans are reviewed: definite associations with cancer of the urinary bladder, lymphatics, stomach, lung, and perhaps, other sites, have been made. (367 Refs)

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As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. ASBESTOS CARCINOGENESIS: ASBESTOS INTERACTIONS AND EPITHELIAL LESIONS IN CULTURED HUMAN TRACHEOBRONCHIAL TISSUES AND CELLS.
Haugen A, Harris C
Div. Cancer Cause and Prevention, NCI, Bethesda, MD
Recent Results Cancer Res; 82:32-42 1982

2. REVIEW: ORAL CONTRACEPTIVES AND MENOPAUSAL ESTROGENS IN RELATION TO BREAST NEOPLASIA.
Brzezinski A, Schenker JG
Dept. Obstetrics and Gynecology, Hadassah Univ. Hosp., POB 12000, 91120 Jerusalem, Israel
Isr J Med Sci; 18(4):433-438 1982

3. LIVER DISEASES DUE TO HORMONAL CONTRACEPTIVES.
Lie TS
Chirurgische Klinik und Poliklinik, Universitat, Sigmund-Freud-Str. 25, D-5300 Bonn 1, W. Germany
MMW; 124(20):489-494 1982
In GER

RADIATION CARCINOGENESIS

4. THE WORK OF THE NRPB 1977/80 AND A REVIEW OF THE FIRST 10 YEARS.
National Radiological Protection Board
Natl. Radiological Protection Board, Chilton, Didcot, Oxfordshire OX11 0RQ, England
The Work of the NRPB 1977/80 and a Review of the First 10 Years. Chilton, Didcot, Oxfordshire, National Radiological Protection Board, 70 pp., 1981.

DIETARY FACTORS IN CARCINOGENESIS

5. ALCOHOL AND CARCINOGENESIS.
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6. ZINC, COPPER, AND MANGANESE IN IMMUNE FUNCTION AND EXPERIMENTAL ONCOGENESIS.
Beach RS, Gershwin ME, Hurley LS
Dept. Internal Medicine, Div. Rheumatology-Clinical Immunology, Univ. Calif., Davis, CA, 95616
Nutr Cancer; 3(3):172-191 1982

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

7. TRENDS IN CANCER INCIDENCE: CAUSES AND PRACTICAL IMPLICATIONS. PROCEEDINGS OF A SYMPOSIUM HELD OSLO, NORWAY, 6-7 AUGUST 1980.
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Peto R, Schneiderman M
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9. NASAL CARCINOMA IN WOODWORKERS: A REVIEW.
Wills JH
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16. ROLE OF ENZYMATIC METHYLATION OF DNA IN CELL DIFFERENTIATION AND TRANSFORMATION.
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17. HYDROGEN ION DYNAMICS AND CANCER: AN APPRAISAL.
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18. CARCINOGENESIS AND BIOLOGICAL EFFECTS OF TUMOR PROMOTERS.
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21. MOLECULAR EPIDEMIOLOGY AND CARCINOGEN-DNA ADDUCT DETECTION: NEW APPROACHES TO STUDIES OF HUMAN CANCER CAUSATION.
Perera FP, Weinstein IB
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J Chronic Dis; 35(7):581-600 1982

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Environmental Mutagen Information Center, Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
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